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# New Syntheses of Diaryl Ethers, Tyrosinols, B-Hydroxytyrosinols, L,L-Isodityrosinol and L,L-Isodityrosine-Derived Agents via the Diels-Alder Reaction

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# NEW SYNTHESES OF DIARYL ETHERS, TYROSINOLS, β-HYDROXYTYROSINOLS, L,L-ISODITYROSINOL AND L,L-ISODITYROSINE-DERIVED AGENTS VIA THE DIELS-ALDER REACTION

by

Xianqi Feng

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of the requirements of the degree

of

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in

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1992

I hear, and I forget.

I see, and I remember.

I do, and I understand.

Ancient Chinese Proverb

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Xianqi Feng

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| [α] | Specific rotation [expressed without units; the actual units, deg mL/(g dm), are understood] |
| Ac | acetyl |
| AIBN | 2,2'-azobisisobutyronitrile |
| anhyd | anhydrous |
| Ar | aryl |
| atm | atmosphere(s) |
| Bn | benzyl |
| BOC, Boc | *tert*-butoxycarbonyl |
| bp | boiling point |
| br | broad (spectral) |
| Bu | butyl |
| *s*-Bu | *sec*-butyl |
| *t*-Bu | *tert*-butyl |
| °C | degree Celsius |
| calcd | calculated |
| CBZ, Cbz | benzyloxycarbonyl |
| cm | centimeter(s) |
| concd | concentrated |
| Cp | cyclopentadienyl |
| δ | chemical shift in parts per million downfield from tetramethylsilane |
| d | day(s), double (spectral) |
| DCC | N,N-dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |

| | |
|---|---|
| de | diastereomeric excess |
| DIBALH | diisobutylaluminum hydride |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | dimethylformamide |
| DMP | 2,2-dimethoxypropane |
| DMSO | dimethyl sulfoxide |
| EDCI | 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide |
| ee | enantiomeric excess |
| equiv | equivalent |
| Et | ethyl |
| FT | Fourier transform |
| g | gram(s) |
| h | hour(s) |
| Hz | hertz |
| IR | infrared |
| *J* | coupling constants |
| k | kilo |
| L | liter(s) |
| LDA | lithium diisopropylamide |
| μ | micro |
| m | multiplet (spectral), meter(s), milli |
| M | mole per liter |
| Me | methyl |
| MHz | megahertz |
| min | minute(s) |
| mM | millimoles per liter |
| mol | mole(s) |

| | |
|---|---|
| mp | melting point |
| MTPA | α-methoxy-α-(trifluoromethyl)phenylacetic acid |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| ot | oven temperature (in kugelrohr distillations) |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| ppm | parts per million (in NMR) |
| PPTS | pyridinium *p*-toluenesulfonate |
| Pr | propyl |
| *i*-Pr | isopropyl |
| q | quartet (spectral) |
| quant | quantity |
| $R_f$ | retention factor (in chromatography) |
| rt | room temperature |
| s | singlet (NMR); second(s) |
| t | triplet (spectral) |
| TBDMS | *tert*-butyldimethylsilyl |
| TEA | triethylamine |
| Tf | trifluoromethanesulfonyl (triflyl) |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl, tetramethylsilane |
| Torr | 1 atm |

| | |
|---|---|
| Ts | tosyl, *p*-toluenesulfonyl |

# ABSTRACT

New Syntheses of Diaryl Ethers, Tyrosinols, β-Hydroxytyrosinols, L,L-Isodityrosinol and L,L-Isodityrosine-derived Agents via the Diels-Alder Reaction

by

Xianqi Feng, Doctor of Philosophy
Utah State University, 1992

Major Professor: Dr. Richard K. Olsen
Department: Chemistry and Biochemistry

Syntheses of diaryl ethers were approached by use of a Diels-Alder reaction employing a new type of diene attached with an aryloxy group. Thus, 2-methyl-3-phenoxybutadiene (**90b**), 2-methoxy-3-phenoxybutadiene (**92b**) and (4S)-3-(t-butyloxycarbonyl)-2,2-dimethyl-4-[4-(3-methoxy-1,3-butadienyl-2-oxy)phenylmethyl]oxazolidine (**93b**) were synthesized in ~65% yields by methylenation of the carbonyl function in the corresponding 2-substituted acrylate aryl ester using Tebbe's reagent. The 1,3-bis[(trimethylsilyl)oxy]-2-phenoxybutadiene (**105**) was made from 1-phenoxy-2-propanone (**101**) by a sequence of formylation and enolsilylation. Methyl propiolate (**107**) and dimethyl acetylenedicarboxylate (**113**) were heated at reflux with diene **90b** and **92b** in toluene to provide the cyclohexadiene adducts, which

were easily oxidized to the corresponding diaryl ethers using DDQ in ~90% yields. Alkyne **107** was also reacted with diene **105** to provide 3-hydroxy-4-phenoxybenzoic acid methyl ester (**116**) in 49% yield. The diaryl ethers were characterized by IR, $^{1}H$ NMR, $^{13}C$ NMR and elemental analyses.

N-Cbz-O-methyl-L-tyrosinol (**129a**) and (1R,2R)-N-Cbz-O-methyl-β-hydroxytyrosinol (**136b**) were synthesized by the condensation of Danishefsky's diene (**124**) with an acetylenic ketone, benzyl (R)-4-(1-oxo-2-propynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (**120**), which was derived from D-serine. Reduction of the ketone function in the adduct using $NaBH_4$ at 0 °C provided **136b**. Deoxygenation of the alcohol function in **136b** via Barton's procedure gave the optically pure tyrosinol **129a**.

The synthesis of the fully differentiated (L,L)-isodityrosinol, (4R)-3-benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-[(2S)-2-(t-butyloxycarbonyl)amino-3-hydroxypropyl]phenoxy]-4-methoxyphenylmethyl]oxazolidine (**169**) was also approached by a sequence of cycloaddition, aromatization and reduction. The cycloaddition between ketone **120** and diene **93b** resulted in formation, in 91% yield, of an equal mixture of two regioisomers that were separated by flash chromatography on silica gel. The aromatization of the required cyclohexadiene adduct using DDQ gave (4R)-3-benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-t-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl phenoxy]-4-methoxyphenyloxo] oxazolidine (**145a**), which was a precursor to isodityrosinol **169**. The fortuitous selective methanolysis of one of the oxazolidine rings in **145a** and reduction of the ketone function in

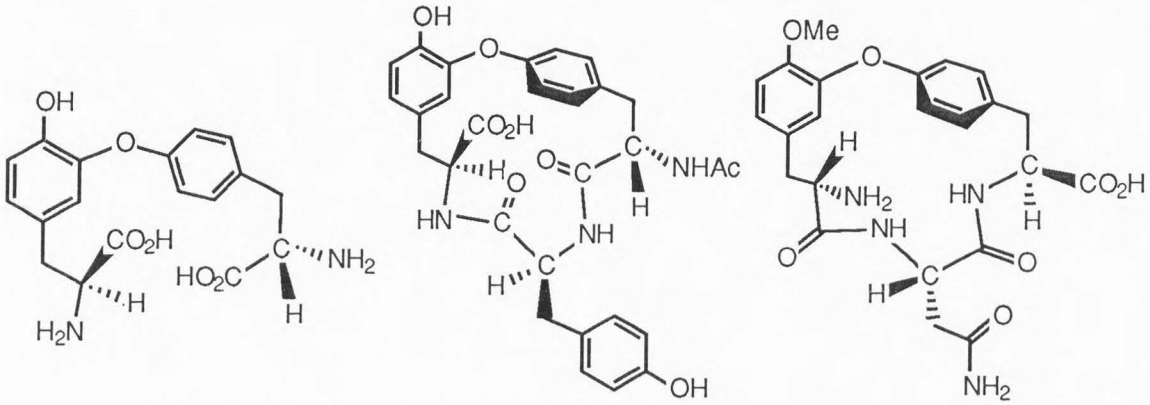
the resulting monoalcohol via Barton's procedure gave isodityrosinol **169** in good overall yield (37%). The structure of isodityrosinol **169** was confirmed by $^{1}H$ NMR, $^{13}C$ NMR, IR and elemental analyses. The diastereomeric purity of isodityrosinol **169** was proved by use of Mosher's acid.

A new synthetic approach to K-13 was also described. Isodityrosinol **169** was oxidized by $RuCl_3$ + $NaIO_4$, followed by coupling with tyrosine methyl ester to provide, in 56% overall yield, N-[N-(t-butyloxy)carbonyl]-O-[(R)-5-(3-benzyloxy carbonyl-2,2-dimethyloxazolidin-4-yl-methyl)-2-methoxyphenyl]-L-tyrosyl]-O-methyl-L-tyrosine α-methyl ester (**174**), which was a precursor to K-13. Cyclization of the resulting amino acid derived from the tripeptide **174** was unsuccessful, and more research on the cyclization is needed.

(126 pages)

## GENERAL INTRODUCTION

The construction of a diaryl ether bond containing an amino acid side chain poses a challenge[1] in organic synthesis. Diaryl ether is not only a basic constituent of many important proteins but also an essential unit in the tyrosine-derived peptides[1-4] (Figure 1, isodityrosine (**1**),[2] K-13 (**2**)[1,3] and OF4949-III (**3**)[1,4]) and β-hydroxytyrosine-derived peptides (Figure 2, β-hydroxyisodityrosine (**4**),[5] 3-chloro-β-hydroxytyrosines **5** & **6**,[6] bouvardin (**7**),[7] RA IV (**8**)[5] and vancomycin tripeptide **9**[6]).

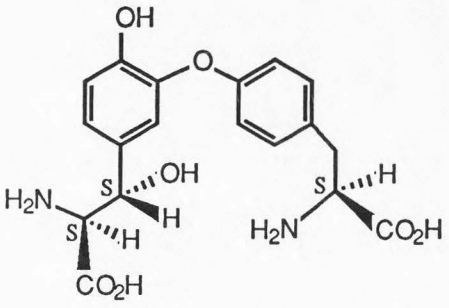



**1** L, L-Isodityrosine **2** K-13 **3** OF4949-III

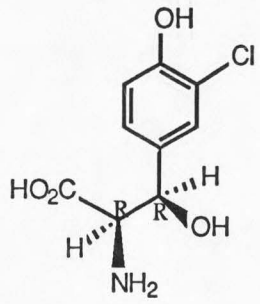
**Figure 1.** Structures of tyrosine-derived agents.

Recently, a number of research groups[8] have been researching the synthesis of a fully differentiated isodityrosine containing oxidatively coupled aromatic nuclei. The most widely used methodology was the classical Ullmann reaction.[1,2,3] Boger and Yohannes[2a,8,9] have applied their optimal Ullmann coupling reaction involving reactants with an amino acid chiral center for the direct synthesis of K-13 and OF4949 III. Evans and co-workers[1] have also

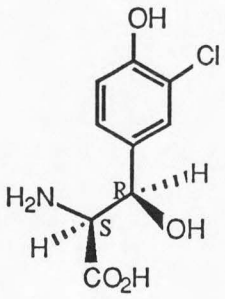
employed a more optimal Ullmann coupling partner without any amino acid side chains, followed by the introduction of chiral auxiliaries in ten synthetic steps to give the final isodityrosine.



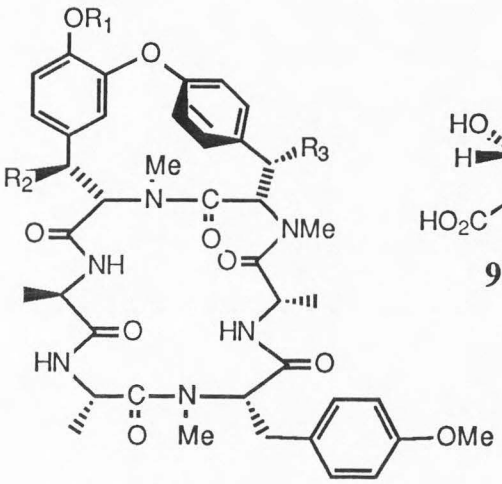
**4** 3-[4-(S)-[2-Amino-2-hydroxycarbonyl)ethyl]-phenoxy-(S)-β-hydroxy-L-tyrosine

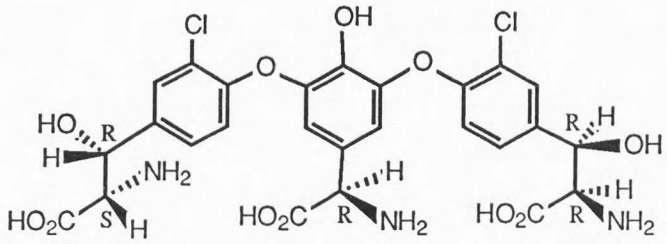


**5** 3-Chloro-β-(R)-hydroxy-D-tyrosine



**6** 3-Chloro-β-(R) hydroxy-L-tyrosine





**9** Vancomycin's tripeptide(above)

| $R_1$ | $R_2$ | $R_3$ | (left) | |
|---|---|---|---|---|
| H | H | OH | Bouvardin | **7** |
| Me | OH | H | RA-IV | **8** |

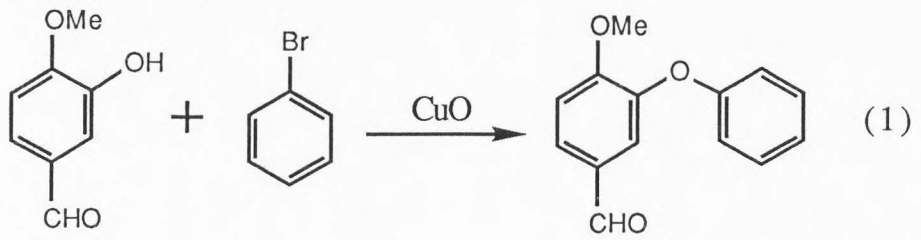
**Figure 2.** Structures of β-hydroxytyrosine-derived agents.

The novel aspect of this study was to explore a different approach to the syntheses of the differentiated isodityrosinol and its derived agents (Figure 1) by employing a classical Diels-Alder reaction.

# LITERATURE REVIEW

## Diaryl Ethers

Synthesis of diaryl ethers can be approached by a classical Ullmann reaction.[10] Condensation of an aryl halide with a nucleophilic phenol in the presence of $K_2CO_3$ and cupric oxide provides diaryl ethers in ~50% yield. For example, in the preparation of O-phenylisovanillin **12**, strong basic reaction conditions ($K_2CO_3$, 150 °C, eq 1) were employed.




(1)

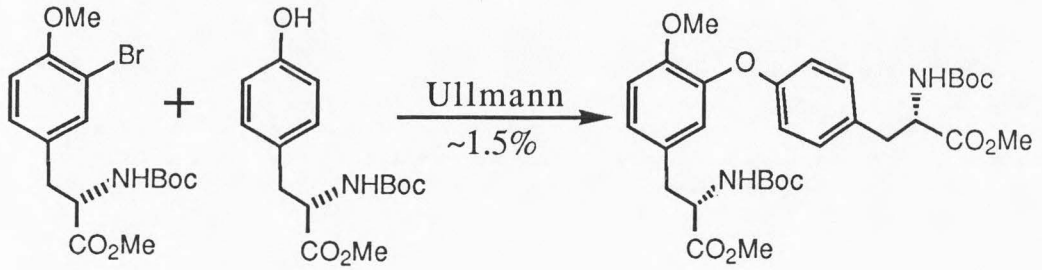
**10** **11** **12** O-Phenylisovanillin

The reaction conditions were also modified by use of a catalytic amount of CuO in the presence of pyridine. The yields range from 42% to 51%. However, such conditions can not be used widely in the synthesis of multisubstituted diaryl ethers because of the harsh reaction conditions required and the variable yields obtained (for example, the 1.5% yield obtained in eq 2).

## L,L-Isodityrosine in a Fully Differentiated Form

**General Synthesis.** The synthesis of isodityrosine in a fully differentiated form has been examined by a number of research groups in recent years. The first synthesis (eq 2) was reported in

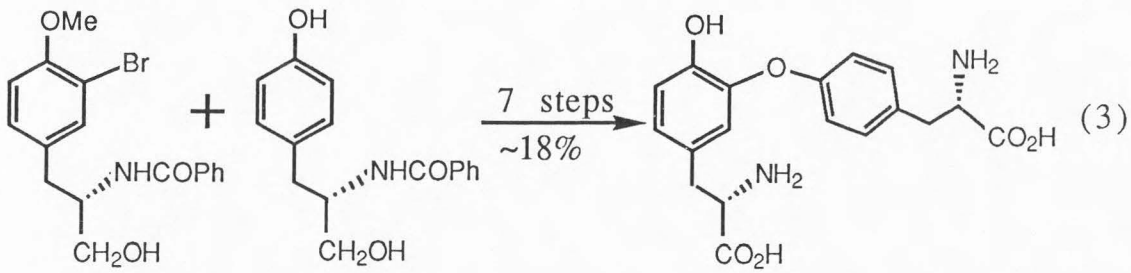
1987 by Yasuzawa.[11] N-Boc-3-Bromotyrosine methyl ester (**13**) was reacted with N-Boc-tyrosine methyl ester (**14**), generating only a 1.5% yield of isodityrosine **15** in an undifferentiated form using classical Ullmann reaction conditions. From the practical point of view, modified reaction conditions need to be developed for this type of synthetic approach.




(2)

**13** **14** **15**

In 1989, Jung's research group[2b] reported a method for the synthesis of L,L-isodityrosine (**1**). Condensation of two protected amino alcohols **16** and **17** under Ullmann coupling conditions (37-42% yields), followed by Jones' oxidation, provided an undifferentiated isodityrosine (**1**) in 18% overall yield.



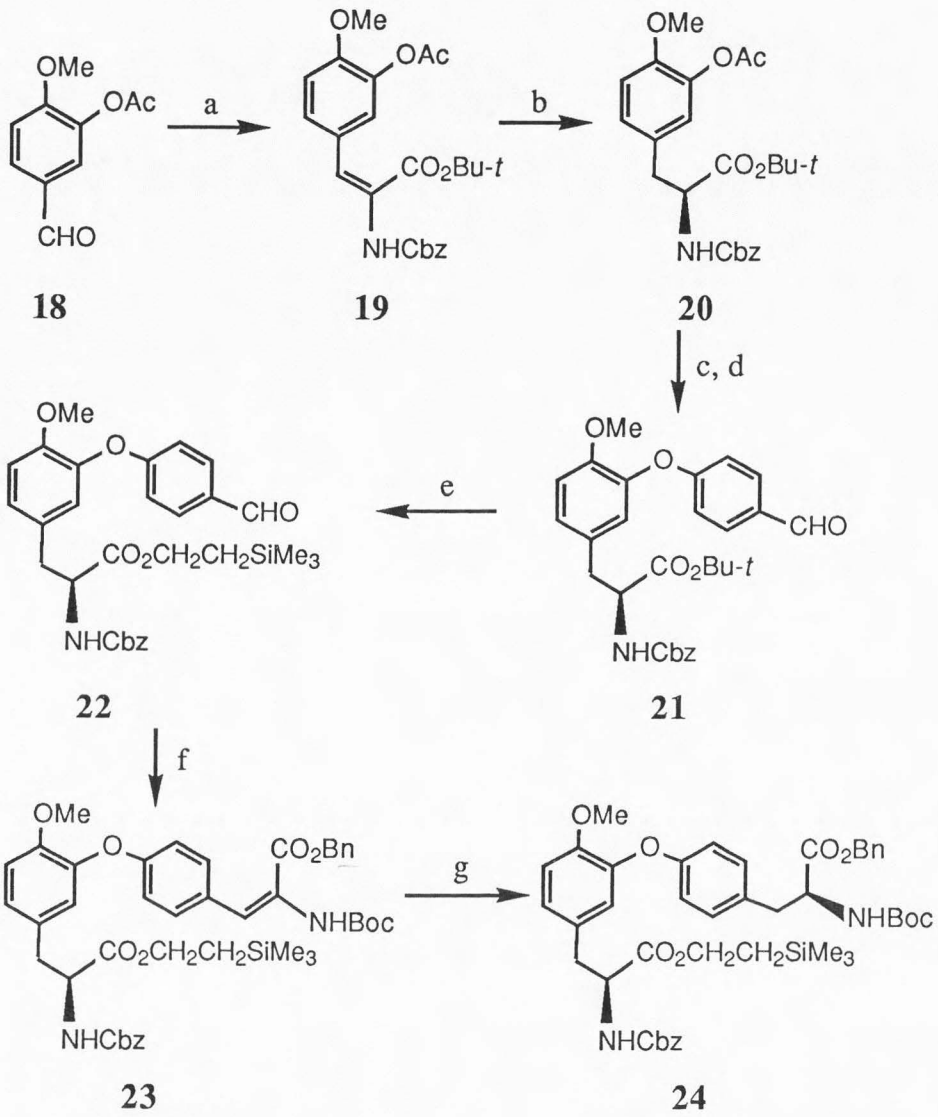

(3)

**16** **17** **1**

**Schmidt's Research.** As the isodityrosine (**1**) in its undifferentiated form is almost of no value in the synthesis of isodityrosine-derived agents (Figure 1), the first synthesis of

isodityrosine **24** in a fully differentiated form (Scheme I) was reported by Schmidt's research group[4a] in 1988.

**Scheme I**[a]



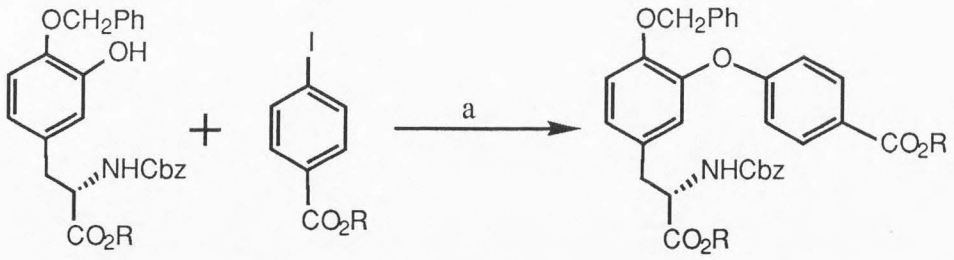

[a] (a) N-benzyloxycarbonyl-2-dimethyoxyphosphoryl-glycine *t*-butyl ester, KOBu-*t*, $CH_2Cl_2$, -60~25 °C, 12 h, 70%; (b) $[Rh(DIPAMP)]^+$, $H_2$, MeOH, 20 °C, 75 h, quant; (c) NaOH, MeOH, 20 °C, 15 h, 86%; (d) p-bromobenzaldehyde, CuO, $K_2CO_3$, Py, 130 °C, 12 h, 93%; (e) 1. $CF_3CO_2H$, 20 °C, 5 h; 2. DCC, 2-trimethylsilylethanol, DMAP, ethyl

acetate, -10~20 °C, 12 h, 75%; (f) N-*t*-butyloxycarbonyl-2-dimethoxy phosphoryl-glycine benzyl ester, KOBu-*t*, $CH_2Cl_2$, -60~20 °C, 12 h, 73%; (g) $[Rh(DIPAMP)]^+$, $H_2$, MeOH, 20 °C, 75 h, quant.

The overall yield for the final isodityrosine **24** was less than 20%. The key synthetic methods in this route were two asymmetric hydrogenations using a rhodium metal complex as the catalytic species.

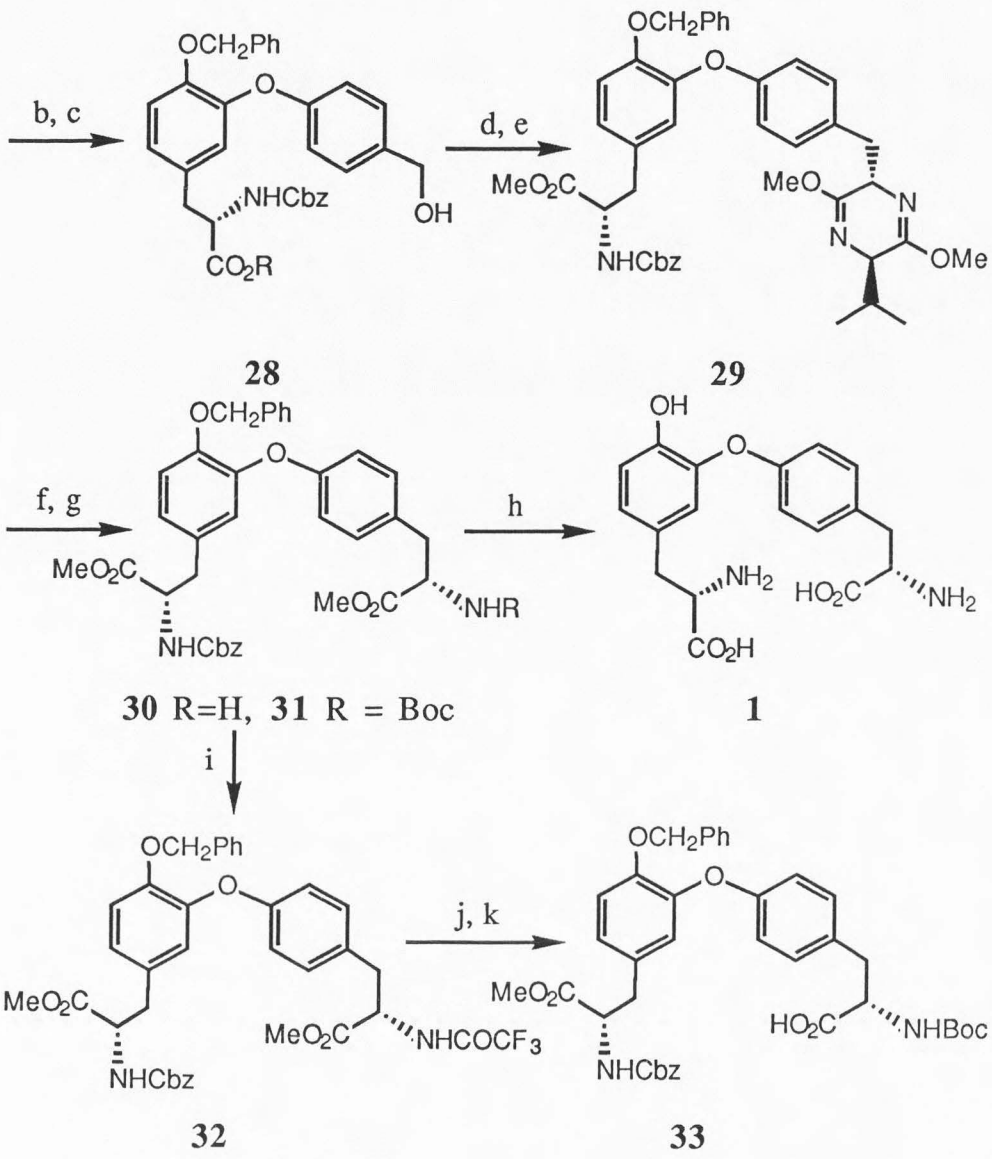
**Boger's Research.** Boger and Yohannes[3] (Scheme II) have developed their optimal Ullmann coupling reaction conditions for the synthesis of diaryl ethers. A differentiated L-Dopa **25** with 90%ee reacted with an aromatic halide **26** under a suitably mild reaction condition (130 °C, NaH, nitrobenzene, a special optimal condition for L-Dopa **25**) to provide a key precursor **27** in 50% yield with 88%ee optical purity. Introduction of another chiral amino acid center to the L-Dopa derivative **28** was successfully achieved by using Schöllkopf's reagent.[3,4b] The final differentiated isodityrosine **33** with 80%de was obtained in more than ten steps and in 10~15% overall yield. The isodityrosine (**1**) was also obtained by exposing **31** to strong acidic conditions (6.0 N HCl).

**Scheme II**[a]




**25** **26** R=*t*-Bu **27**

## Scheme II (con't)

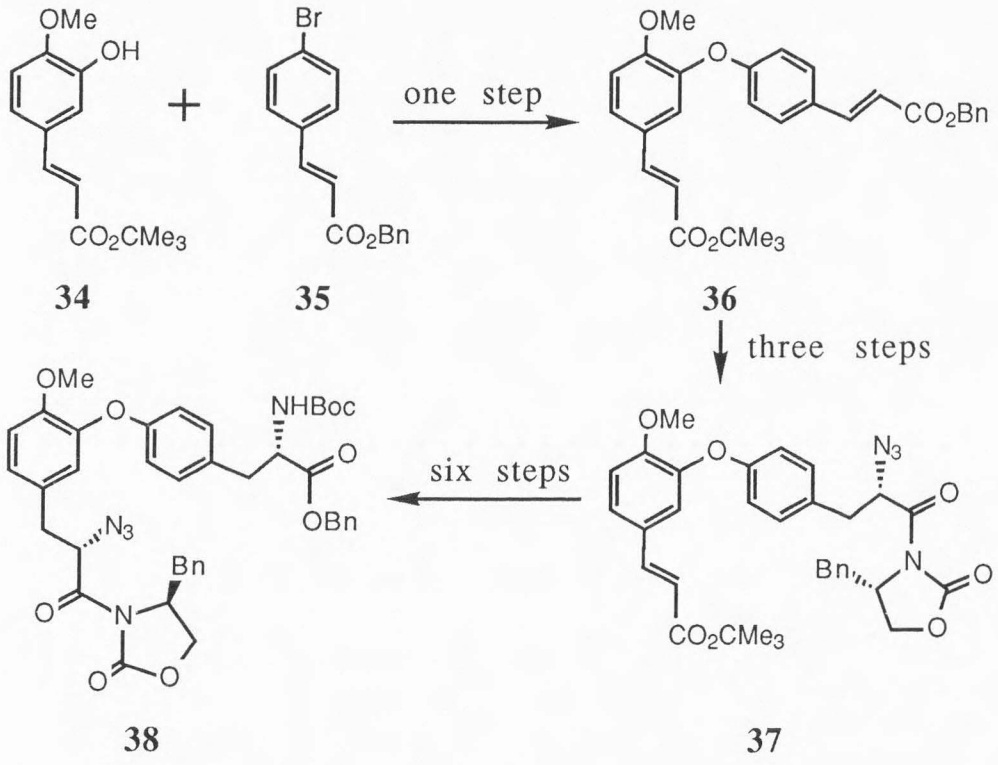



[a] (a) NaH, CuBr, $C_6H_5NO_2$, 130 °C, 8 h, 46%; (b) 3.0 M HCl/EtOAc, 25 °C, 1.5 h, 95%; (c) 1.0 M $BH_3$/THF, 0 °C, 3 h, 89%; (d) $CBr_4$, $Ph_3P$, $Et_2O$, 25%, 25 °C, 72%; (e) NaH, THF, 0 °C, 5 min; 1.2 equiv of Schöllkopf's reagent, THF, -78 °C, 14 h; (f) 0.5 N HCl (aq)/THF, 25 °C, 57%; (g) $(Boc)_2O$, $K_2CO_3$, THF, 25 °C; (h) 6.0 N HCl, 65 °C, 6 h; (i) $(CF_3CO_2)_2O$, THF, 25 °C, 1 h, 97%; (j) 1.0 equiv of NaH, THF, 25 °C, 1 H, 68%; (k) 1. 10% $K_2CO_3$/MeOH-$H_2O$ (5:2), 25 °C, 6 h, 86%; 2. $(Boc)_2O$, $K_2CO_3$, THF, 25 °C, 2 h, 91%.

In this synthesis, the diphenyl ether bond in **27** was formed in a reaction in which one reactant contained an amino acid side chain.

**Evans' Research.** Evans and co-workers[1] also employed an Ullmann coupling reaction to form the diphenyl ether subunit in **36** prior to the construction of either of the amino acid chiral centers. The introduction of the two stereocenters by use of chiral auxiliaries in ten additional synthetic steps gave the useful isodityrosine **38** (Scheme III) in a better overall yield (~40%).

**Scheme III**

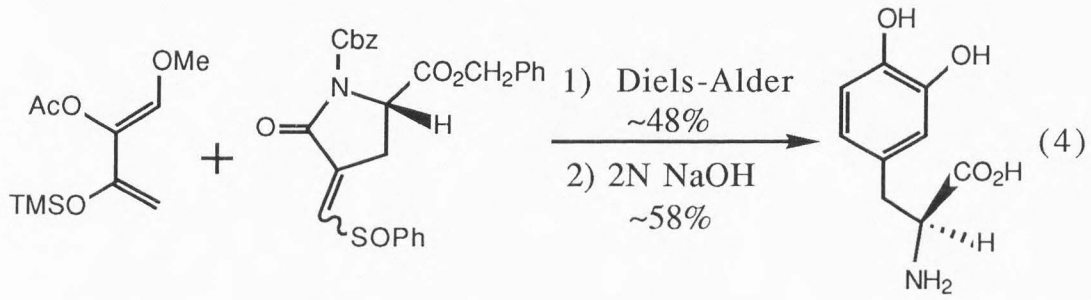



Although Yamamura[12] used another oxidative phenolic coupling methodology in the synthesis of K-13 and piperazinomycin, low yields greatly decreased the practical utility of this approach. From a synthetic point of view, the classical Ullmann reaction is an

attractive yet limited methodology for construction of diaryl ethers, isodityrosine and isodityrosine-derived peptides. Therefore, development of improved new methodology in this area would be highly desirable, a subject that will be discussed in this dissertation.

## Optically Specific Conversion of Dienophile Having an Amino Acid-derived Chiral Center

About one decade ago, Danishefsky[13] developed a new type of dienophile **40** that was derived from L-glutamatic acid. Optically pure phenylalanine, tyrosine and L-Dopa were prepared by condensation of the above dienophile with a variety of dienes.




(4)

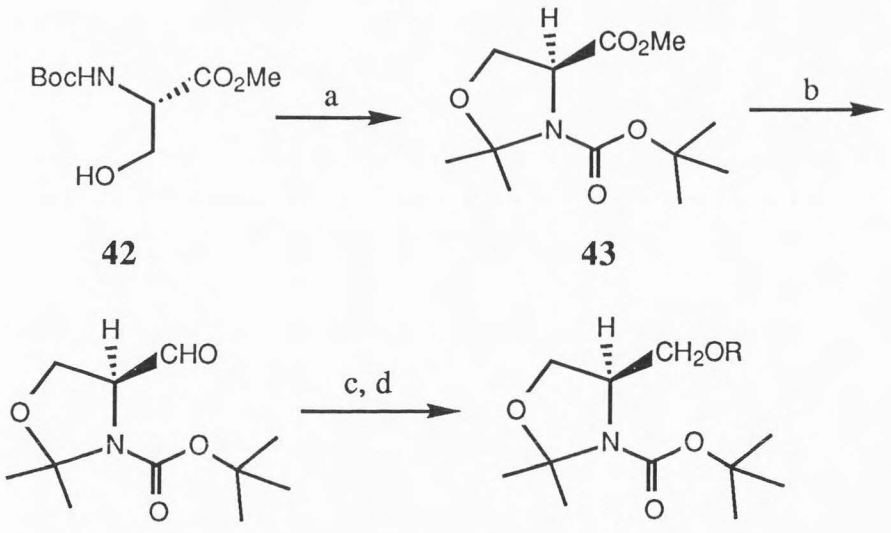
**39** **40** **41**

An example of this synthetic approach to the medicinally important L-Dopa **41**, which was an essential material for the synthesis of isodityrosine, K-13 and OF4949, is shown in eq 4. The key compound in this synthetic procedure was the 1,2,3-trioxygenated diene **39,** which provided in the Diels-Alder reaction the same regiocontrol as the well-known 1,3-bisoxygented dienes.[13] The integrity of the α-stereocenter in dienophile **40** during the course of the Diels-Alder reaction was completely transferred into the final L-Dopa **41**. The overall yield of the preparation was ~30%.

## Optically Pure Serine-derived Oxazolidine Aldehyde as a Nonracemic Synthon

In 1987, Garner and Park[14] developed a new type of nonracemic α–amino aldehyde synthon **44** that was derived from either optically pure D-serine or L-serine. The oxazolidine ring in either aldehyde was found to be stable to racemization during typical laboratory manipulations (vacuum distillation and flash chromatography). The N-Boc serine methyl ester (**42**) was converted into the oxazolidine derivative **43**. The reduction of the ester in **43**, using DIBALH at low temperature, generated the chiral α-amino aldehyde **44**, which is a well-known nonracemic synthon (Scheme IV).

**Scheme IV**[a]



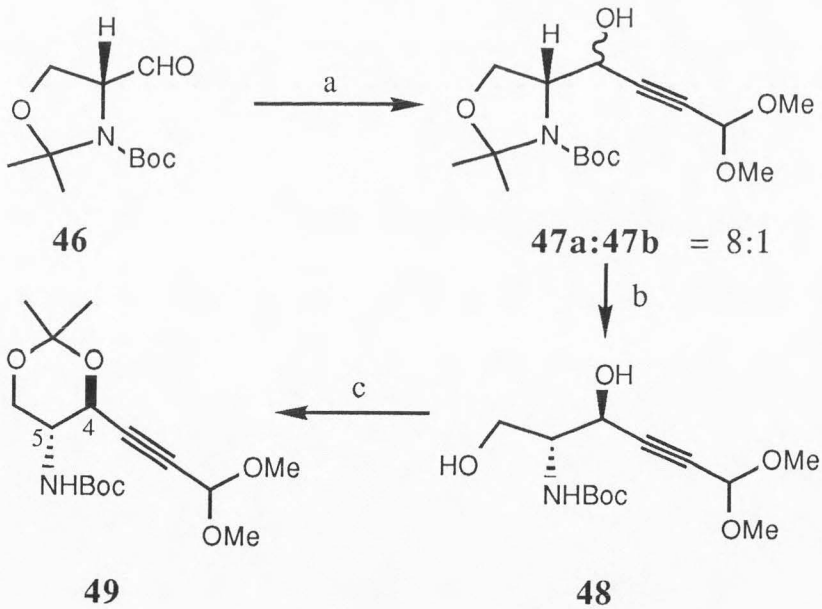

[a] (a) DMP, TsOH, $C_6H_6$, 85%; (b) DIBALH, PhMe, -78 °C, 80%; (c) $NaBH_4$; (d) (S)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), DCC, DMAP.

To measure the optical purity of the aldehyde, the authors reduced the aldehyde **44** with $NaBH_4$ into the primary alcohol **45a**, which was coupled with (S)-Mosher's acid to yield only one diastereoisomer **45b**. In this dissertation, the aldehyde **78**, with an N-Cbz protecting group rather than a Boc group, was used as a chiral, nonracemic starting material.[15a]

## Stereochemistry of Dioxane 49

Garner's research group[16] recently reported the following example. Addition of the lithio derivative of propioaldehyde dimethyl acetal to aldehyde **46** provided alcohol **47a** (*erythro*-) as the major product, with the other diastereomer **47b** (*threo*-) as the minor product. Separation of the two diastereomers (ratio = 8:1) was achieved by use of a chromatographic column.

**Scheme V**[a]



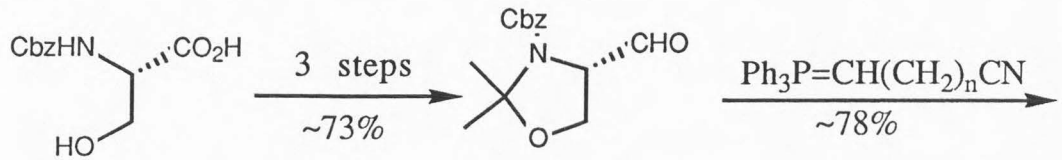

**46** **49** **48**

[a] (a) $LiC{\equiv}CCH(OMe)_2$, THF, -78 °C, 87% combined yield; (b) TsOH, MeOH, rt, 79%; (c) DMP, TsOH, rt, 41%.

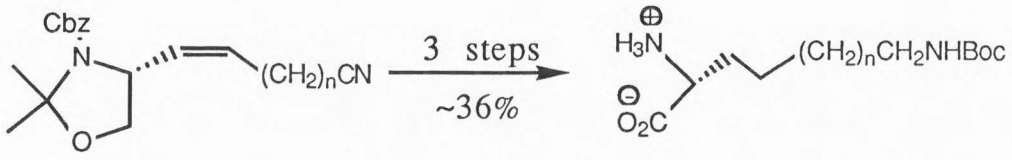
The stereochemical assignments for the two diastereomers were investigated by converting the optically pure alcohol **47a** (the major isomer) into the conformationally well-defined dioxane **49**. A typical *trans*-coupling constant ~8 Hz between $H_4$ and $H_5$ in **49** was observed. In this research, the chemical methodology of the scheme was used to investigate the absolute configuration of β-hydroxytyrosinol.

## Enantiospecific Synthesis of a D-Amino Acid Starting from L-Serine

**Scheme VI**




**50** Cbz-L-Serine **51**



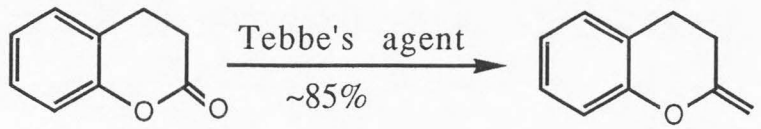

**52** **53** D-$N^{\omega}$-Boc-α, ω-Diaminoalkanoic Acid

An example of an enantiospecific synthesis[15a] of a D-amino acid from serine with L-configuration is shown in Scheme VI. The optically pure aldehyde **51** was obtained from Cbz-L-serine (**50**) in 73% yield. A Wittig reaction afforded Z-alkene **52** in 78% yield. The final D-amino acid **53** was obtained in 95 %ee as determined by $^1H$

NMR spectroscopy of the corresponding Mosher's amide measured at 400 MHz.

## Vinyl Ethers with Aryloxy Groups

Tebbe's reagent[17a] is a well-known reagent for conversion of ketones and esters to olefins and vinyl ethers, respectively. The modified reagent[17b] ($Cp_2TiMe_2$) is an alternative method for this olefination. An example using Tebbe's reagent was reported by Evans' group in 1981.[17c]




(5)

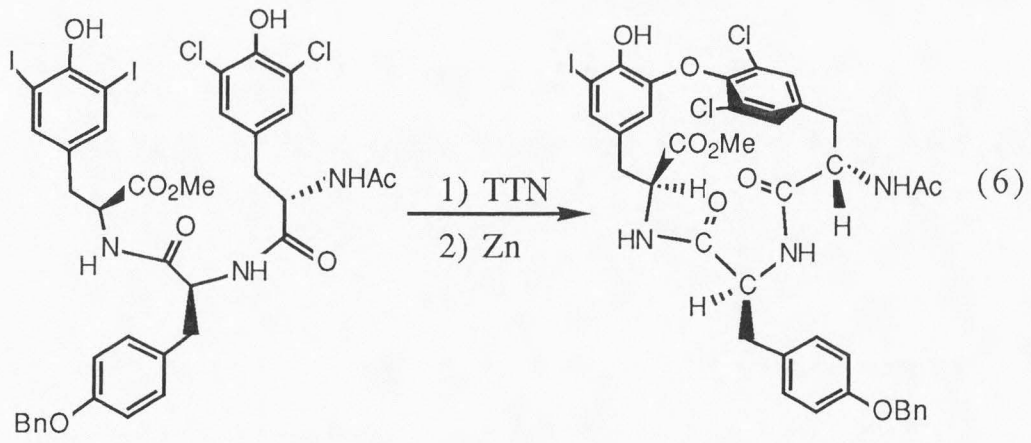
**54** **55**

Aryl enol ether **55** was obtained in 85% yield from the corresponding ester **54**. This thesis used the methylenation methodology for synthesis of dienes with an aryloxy group.

## Isodityrosine-derived Agents K-13 and OF4949-III

**K-13.** An indirect synthesis (eq 6) of K-13 was reported by Yamamura *et al.* in 1989.[12] In the key step, linear tripeptide **56** was subjected to TTN (thallium(III) nitrate) oxidation in MeOH/THF (1:2.5) (-22~25 °C, 9 h), followed by Zn in AcOH (rt, overnight) to give the desired diphenyl ether **57** in 15% overall yield.

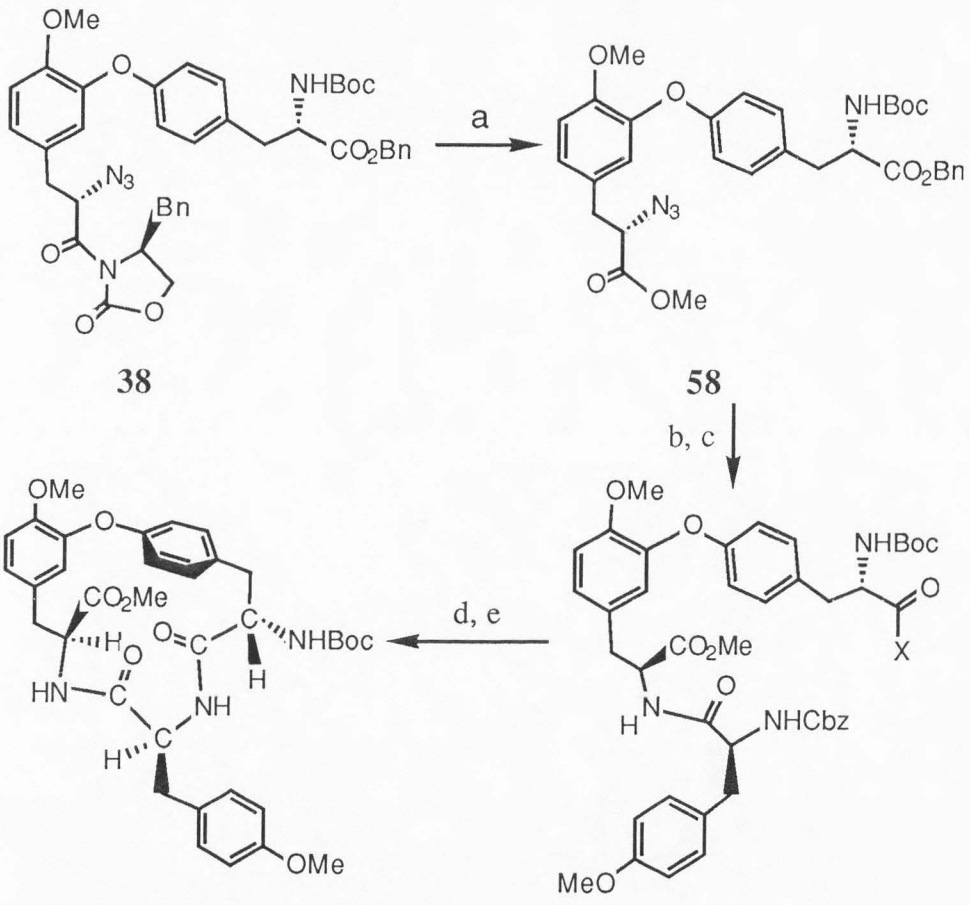
Total direct syntheses of K-13 (**2**) were reported by Schmidt's, Evans' and Boger's research groups. Scheme VII shows the first example of a total synthesis of K-13, which was reported by Evans' research group in 1989.[1]




(6)

**56** **57**

## Scheme VII[a]



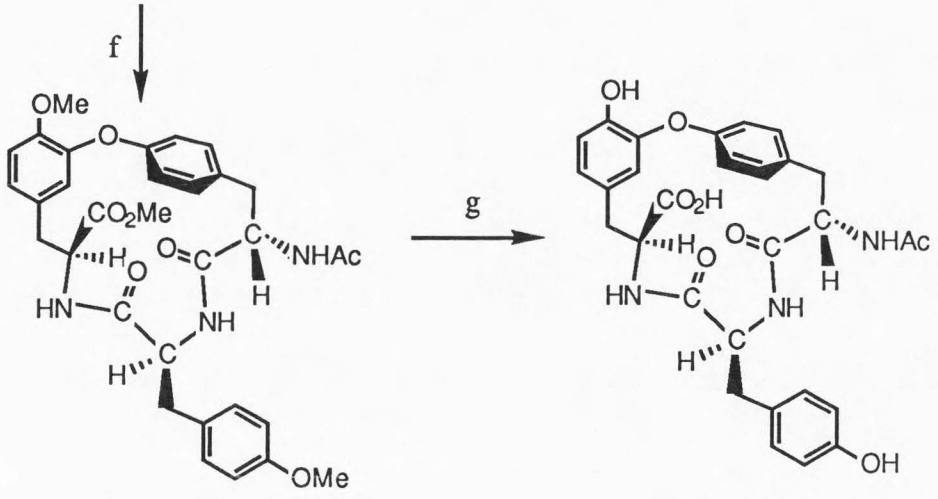

**38** **58**

**60**

**59a** X = OH

**59b** X = $C_6F_5O$

**Scheme VII (con't)**



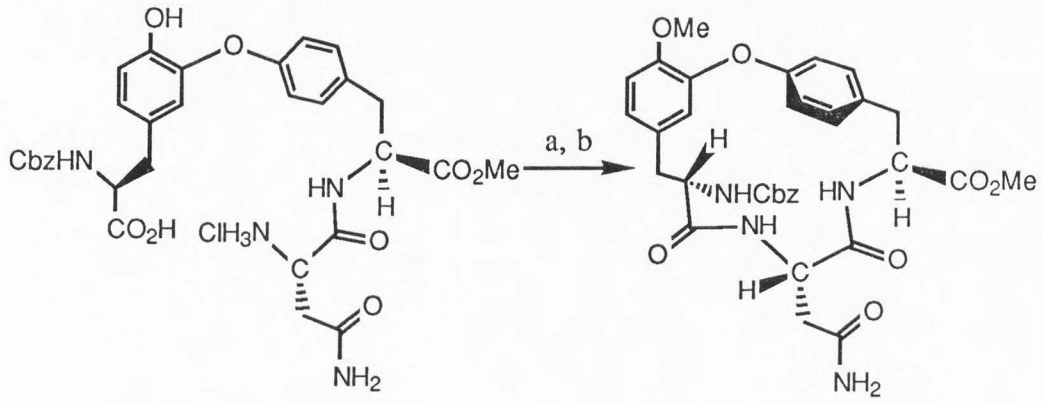

**61** **2** K-13

[a] (a) LiOOH, $CH_2N_2$, 97%; (b) $H_2$, 10% Pd/C; (c) N-Cbz-O-methyl-Tyr-$OC_6F_5$, $NaHCO_3$, 83% combined yield; (d) pentafluorophenol, DCC, 93%; (e) $H_2$, Pd(0), N-methylmorpholine, 2% EtOH/dioxane, 90 °C ; 67%; (f) 1. $CF_3CO_2H$, thioanisole; 2. $Ac_2O$, pyridine, 97%; (g) $AlBr_3$, EtSH, 92%.

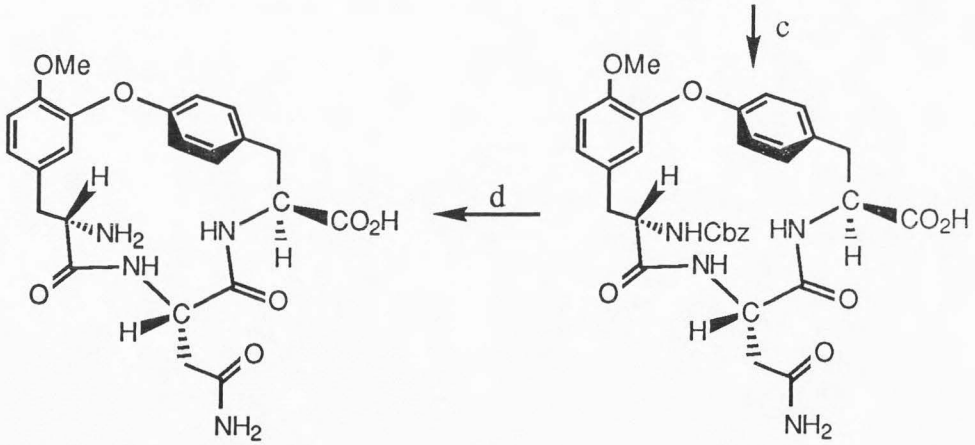
The selectively protected isodityrosine derivative **38** from Scheme III was converted to the methyl ester **58** in 97% yield by a sequence of hydrolysis (LiOOH) of amide **38** and methylation ($CH_2N_2$) of the resulting acid. Reduction of the azide **58** and coupling of the resulting free amino group with N-Cbz-O-methyl-L-tyrosine pentafluorophenyl ester generated a linear intermediate **59a** required for synthesis of K-13. Condensation of the resulting carboxylic acid function with pentafluorophenol afforded a linear tripeptide **59b** with an activated ester group, which was successfully converted into the cyclic product **60** under catalytic hydrogenation in a basic solution using Pd black. The tris-demethylation of **61** resulted in synthetic K-13 (**2**), which was identical to natural K-13.

**OF4949-III.** The first direct total synthesis of OF4949-III was reported by Schmidt's group in 1988.[4a] Shown in Scheme VIII is the total synthesis of OF4949-III, which was reported by Boger's research group.[4b] The linear tripeptide **62** was cyclized by the action of DPPA in DMF (0.008 M) for 72 h in 58% yield, followed by methylation with $CH_2N_2$ to provide the cyclic product **63** in quantitative yield. OF4949-III (**3**) was obtained in high yield by a sequence of hydrolysis and hydrogenation.

**Scheme VIII**[a]




**62** **63**




**3** OF4949-III **64**

[a] (a) 1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0.008 M, 0 °C, 72 h, 58%; (b) $CH_2N_2$, $Et_2O$, 25 °C, 100%; (c) 3.0 equiv of LiOH, THF/$H_2O$/ MeOH, 25 °C, 92%; (d) 1 atm $H_2$, 10% Pd-C, 93%.

## STATEMENT OF THE PROBLEM

(L, L)-Isodityrosine contains a diphenyl ether bond that links two L-tyrosine subunits. In Evans' methodology, the diaryl ether bond was formed by employing two achiral reacting molecules, while Boger's methodology formed the diaryl ether bond by employing only one chiral reacting molecule. The basic synthetic method used for forming the diaryl ether unit in these approaches was the classical Ullmann reaction.

The question arises concerning the compatibility of the amino acid functionality under the harsh reaction conditions (130 °C, NaH) used in Boger's research, and in Evans' research, between the practical utility of the reported method and the multistep synthesis. To solve these problems, the further development of new and modified methodologies for synthesis of diaryl ethers will continue to be an important area of interest.

In this dissertation, a new method for synthesis of diastereomerically pure isodityrosinol and isodityrosine-derived agents was developed. The basic method of this research was a classical Diels-Alder cycloaddition reaction (Figure 3) for forming one of the six membered rings in isodityrosine. Both dienophile and diene in the Diels-Alder reaction were chiral starting materials, compared with Boger and Evans' research; therefore, one chiral amino acid center in (L,L)-isodityrosine was established by enantiospecific conversion from D-serine, while the other center was derived from L-tyrosinol.

The main purpose of this dissertation was to synthesize (L,L)-isodityrosinol in a fully differentiated form (Figure 3). Secondary goals were 1) to develop a new class of dienophiles as chiral synthons for synthesis of diaryl ethers containing the coupled aromatic nuclei; 2) to develop a new type of diene attached with both the simple phenoxy group and the tyrosine moiety; 3) to develop a new methodology for construction of both simple diaryl ethers and a fully differentiated isodityrosinol; 4) to determine the diastereomeric purity of the (L,L)-isodityrosinol; 5) to study the stereoselective reduction of a β-keto tyrosinol derivative for synthesis of β-hydroxytyrosine; and 6) to explore a new synthetic approach to the isodityrosine-derived agents K-13 and OF4949 III.

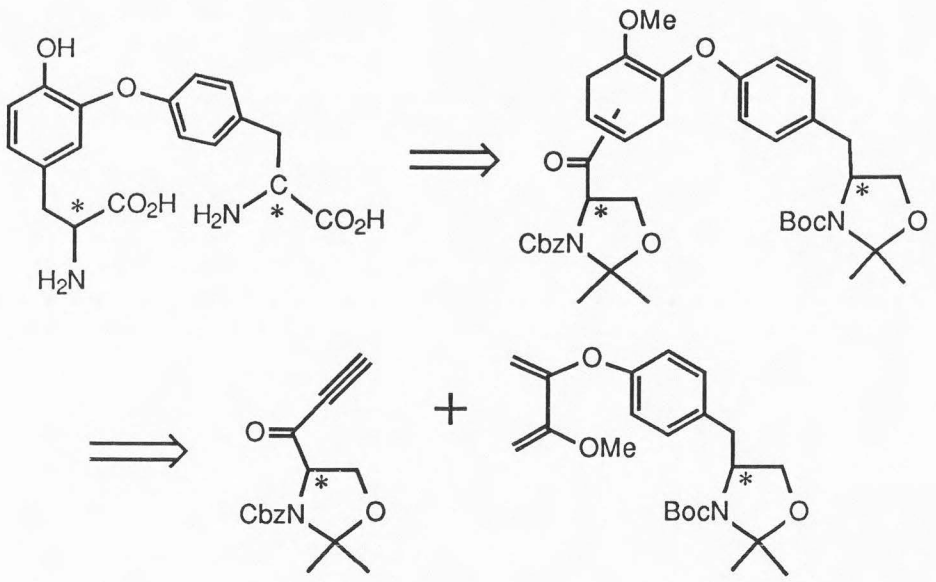


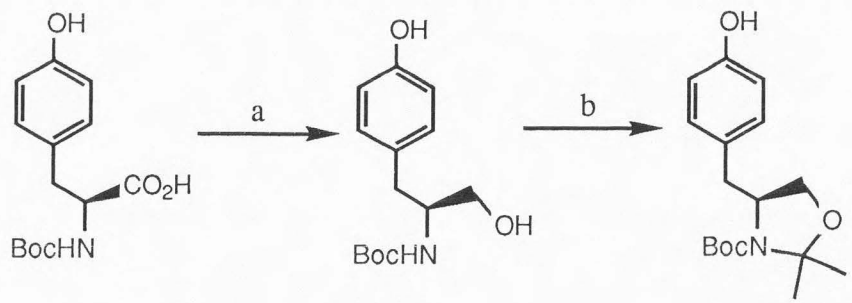

**Figure 3.** Retrosynthesis of isodityrosine via the Diels-Alder reaction.

## RESULTS AND DISCUSSION

### Preparation of Tyrosinol Oxazolidine Derivatives from N-Boc-L-tyrosine and N-Cbz-L-tyrosine

**The Optically Pure N-Boc-L-tyrosinol Oxazolidine Derivative 67.** Synthesis of the chiral diene required for the Diels-Alder reaction (Figure 3) involved the use of an amino alcohol (tyrosinol) as an N-protected amino acid synthon. The chemical procedure in Scheme IX outlines the synthesis of N-Boc-tyrosinol oxazolidine **67**, which is a suitable chiral starting material for providing the tyrosine moiety in the synthesis of the required diene **93b** (eq 9 and 10). The procedure was carried out in two simple steps.[18] One of the two chiral centers in (S,S)-isodityrosinol will be derived from this optically pure oxazolidine **67.**

**Scheme IX**[a]



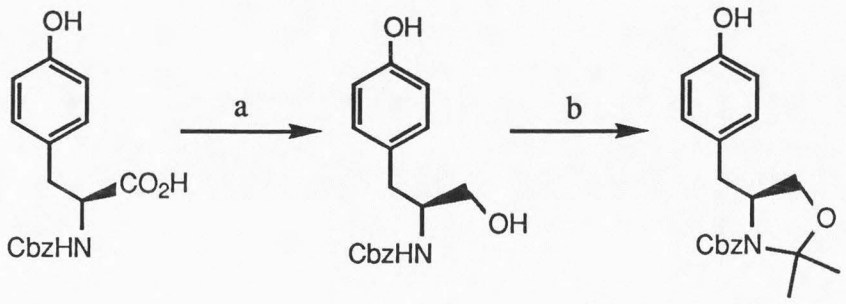

**65** **66** **67**

[a] (a) LAH, ethyl ether, reflux, 4 h, 82%; (b) TsOH, DMP, acetone, rt, overnight, 79-87%.

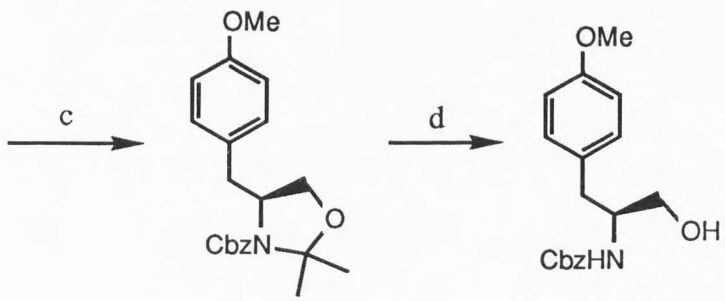
**The Optically Pure N-Cbz-*O*-methyl-L-tyrosinol (72).** The optically pure N-Cbz-*O*-methyl-L-tyrosinol (**72**) and its

oxazolidine derivative **71** were also synthesized in a similar manner[18] (Scheme X).

**Scheme X**[a]




**68** **69** **70**



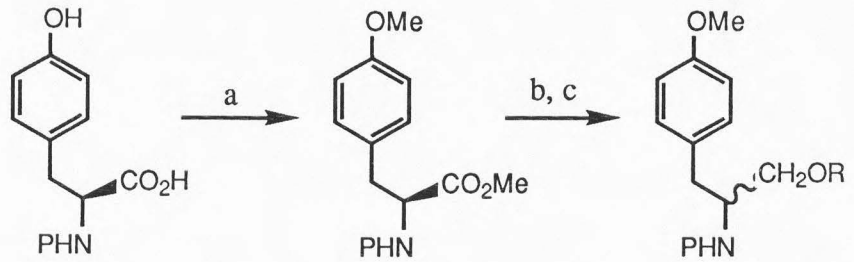

**71** **72**

[a] (a) LAH, THF, reflux, 3 h, 41%; (b) TsOH, DMP, acetone, rt, overnight, 65%; (c) $K_2CO_3$, MeI, DMF, rt, 12 h, 93%; (d) TsOH, MeOH, rt, 12 h, 85%.

**N-Cbz-*O*-methyltyrosinol (74a) with Partial Racemization.** The optically pure N-Cbz-*O*-methyl-L-tyrosine methyl ester (**73a**) and N-Boc-*O*-methyl-L-tyrosine methyl ester (**73b**) were obtained by methylation of the corresponding commercially available tyrosines **68** and **65** according to the standard procedure. Tyrosine **73a** was used to synthesize authentic samples of tyrosinol **74a** and **74b**, whereas tyrosine **73b** was used

to synthesize a key precursor to K-13. Thus, partially racemized N-Cbz-*O*-methyltyrosinol (**74a**) was synthesized by treating the optically pure sample **73a** with NaOMe in MeOH overnight, followed by reduction to the amino alcohol **74a** ([α] -9°). Esterification of the alcohol in **74a** with $Ac_2O$ in $CH_2Cl_2$ containing 1~2 equiv of DMAP provided ester **74b**. Both **74a** and **74b** were partially racemized and were required for subsequent studies to determine optical purity involving the use of Mosher's acid.

**Scheme XI**[a]




**68** P = Cbz **73a** P = Cbz **74a** P = Cbz, R = H
**65** P = Boc **73b** P = Boc **74b** P = Cbz, R = OAc

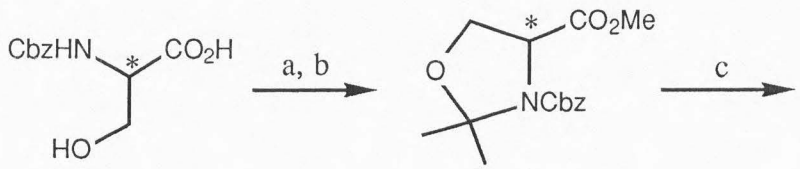
[a] (a) (1) $CH_2N_2$, THF, 0~25 °C; (2) MeI, $K_2CO_3$, DMF, 60 °C, 88%; (b) NaOMe, MeOH, rt, overnight; (c) LAH, ethyl ether, reflux, 3 h.

## Preparation of Chiral Amino Aldehyde from L- or D-Serine

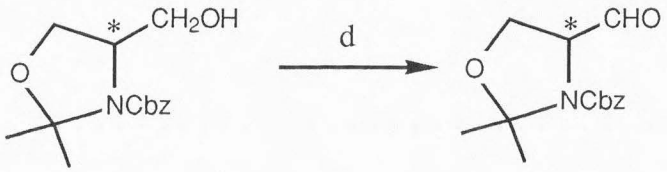
The other chiral amino acid center in (L,L)-isodityrosine was established by enantiospecific conversion from D-serine. The preparation of amino aldehyde **78**, derived from D- or L-serine, was carried out by a known procedure.[15a] Thus, N-Cbz-serine (**75** and **50**) was refluxed in MeOH containing a catalytic amount of TsOH for 2~3 hours. The MeOH was removed in vacuo, the residue was taken

up in acetone containing DMP (5~6 equiv) and the reaction mixture was allowed to stand at rt overnight. Esters **76a** and **76b** were purified by column chromatography. Aldehydes **78a** and **78b** were synthesized by two different methodologies[15a,15b] (Scheme XI and eq 7). The aldehydes **78a** and **78b** obtained from Moffatt/Swern oxidation[15b] of the corresponding alcohols (Scheme XI) had a lower optical value than the samples obtained from a one-step reduction[15a] of the corresponding esters using DIBALH (eq 7).

**Scheme XI**[a]

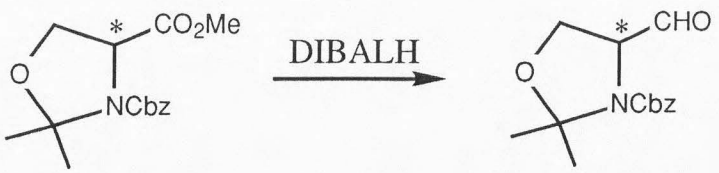



**75** N-Cbz-D-serine **76a** (R)
**50** N-Cbz-L-serine **76b** (S)




**77a** (R) **78a** (R)
**77b** (S) **78b** (S)

[a] (a) MeOH, TsOH, reflux, 3 h; (b) DMP, TsOH, acetone, rt, 12 h; (c) $NaBH_4$, LiCl, MeOH/THF; (d) Moffatt/Swern oxidation.



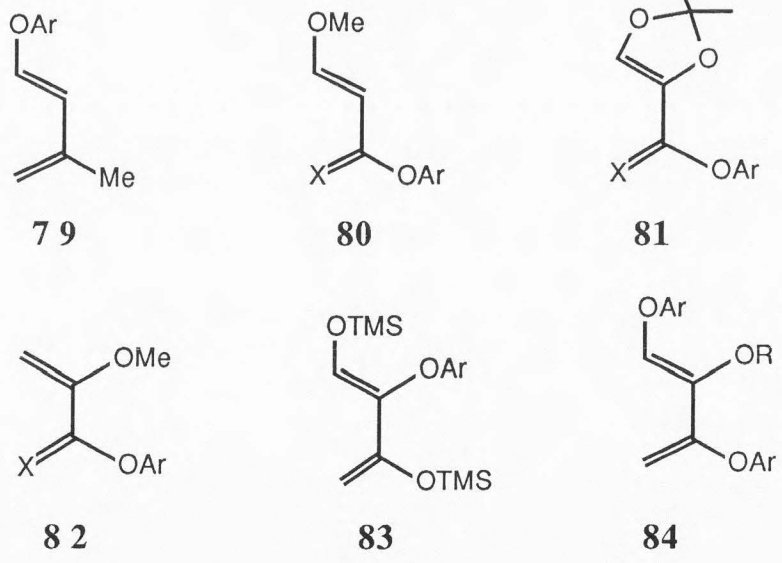

(7)

**76a** (R) **78a** (R)
**76b** (S) **78b** (S)

Both optical rotation values from the two-step process ($\alpha_D$ ±50°) and that from the one-step process ($\alpha_D$ ±58° to ±69°) were lower than the reported value[15a] ($\alpha_D$ ±70°). The question arises concerning the optical purity of the chiral aldehyde **78** obtained by these methods. The detailed chemistry for solving this problem will be discussed later in this dissertation (Scheme XVIII).

## Preparation of New Types of Dienes Attached with Aryloxy Groups

**General Studies.** The selection of an appropriate diene not only affects the reactivity of the Diels-Alder reaction but also the final structure of the diaryl ether unit. Figure 4 Shows several dienes with different functional groups that will serve different research purposes. The basic synthetic methodologies examined in this research for preparation of these dienes were 1) Wittig



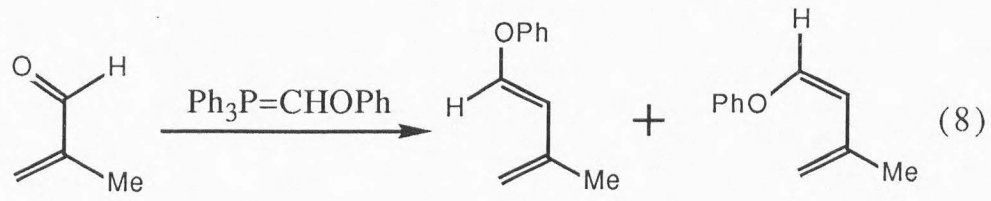

**79** **80** **81**

**82** **83** **84**

**Figure 4.** Structures of different types of dienes.

reaction[19] (**79**), 2) Tebbe's reagent[17a] and the modified reagent[17b] (**80**, **81**, and **82**; X = O to X = $CH_2$) and 3) an enolsilylation reaction[20] (**83** and **84**, R = TMS).

**Wittig Reaction.** A diene with an aryloxy group at the terminal position was made by the Wittig reaction (eq 8). Thus, methacrolein **85** reacted with a Wittig reagent[19] ($Ph_3P$=CHOPh) in benzene at reflux to provide two stereoisomers **86a** and **86b**, which were separated by MPLC on silica gel using hexane as eluent. $^1H$ NMR spectra[21] of these two isomers clearly showed that the coupling constant of *cis*-isomer **86a** was 6.9 Hz, and the coupling constant for the *trans*-isomer **86b** was 12.3 Hz. Studies of these two isomers in Diels-Alder reactions will be discussed in eq 14 and eq 15.




**85** **86a** Trans- **86b** cis-

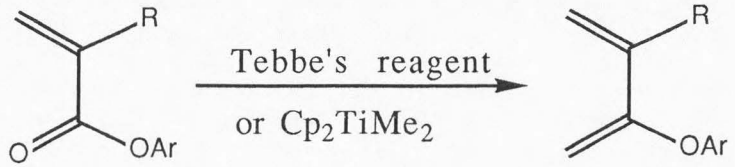

**87** R = Me **89**
**88** R = OMe **67**

**90a-93a**

**Tebbe's reagent and the modified reagent.** The second method for the synthesis of dienes was methylenation of the corresponding α,β-unsaturated esters **90a-93a**. These esters were prepared by a standard esterification reaction[22] (DCC/DMAP) (eq 9).

Methacrylic acid (**87**) was commercially available, and 2-methoxyacrylic acid (**88**) was obtained by the reported procedure.[23]

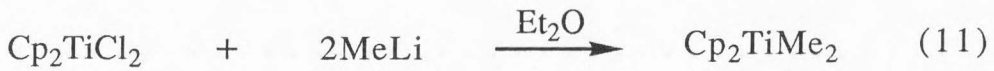
The synthesis of dienes **90b-93b**, using either the modified reagent[17b] ($Cp_2TiMe_2$) or the known Tebbe's reagent,[17a] is demonstrated in eq 10. Because the yield of the reaction using the modified reagent was only 30%, Tebbe's reagent **98** was used to replace the modified reagent, thus providing a 65% yield of diene.



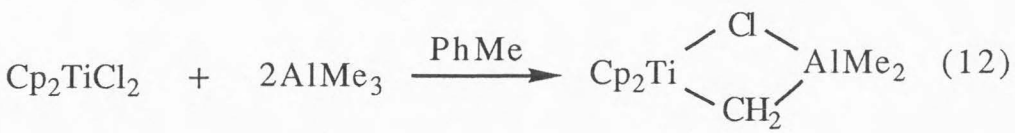

(10)

**90a-93a** **90b-93b**

Preparations of the modified reagent **96** and Tebbe's reagent **98** were obtained by the following two reactions. The modified reagent **96** (eq 11) was developed by Petasis[17b] in 1990, whereas Tebbe's reagent **98** (eq 12) was commercially available.[17a]

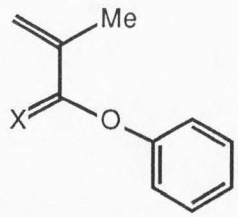



**94** **95** **96** (11)

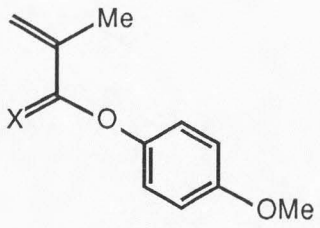



**94** **97** **98** (12)

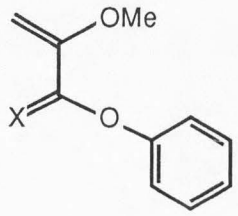
Figure 5 shows the unsaturated esters and the corresponding dienes that were made and used in this research. Structures of most of these esters were confirmed by IR, $^1H$ NMR and $^{13}C$ NMR, and ester **93a** was also confirmed by elemental analysis.



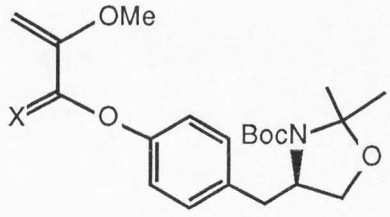

**90a** X = O
**90b** X = $CH_2$




**91a** X = O
**91b** X = $CH_2$




**92a** X = O
**92b** X = $CH_2$

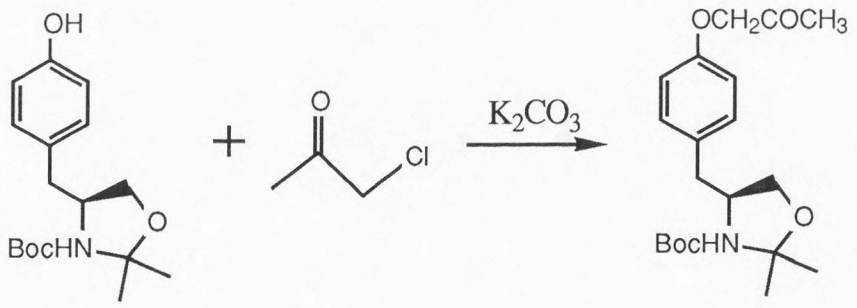



**93a** X = O
**93b** X = $CH_2$

**Figure 5.** Structures of α,β-unsaturated esters and 2,3-disubstituted dienes.

Since the purifications of the dienes were difficult to perform and the dienes were unstable in certain conditions (for example, dimerization and hydrolysis), most of them were only characterized by $^1$H NMR. Dienes **90b-92b** were made for use in the synthesis of less complex diaryl ethers, whereas diene **93b**, with an aromatic amino alcohol, was required for synthesis of (L,L)-isodityrosinol.

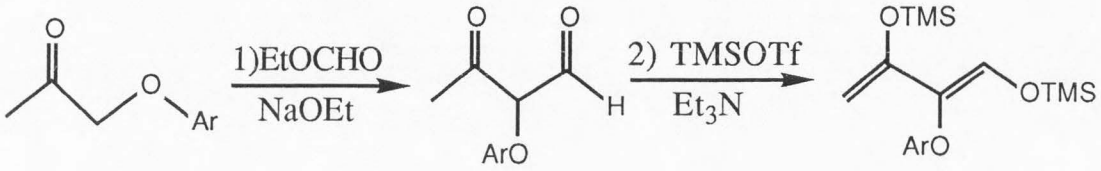
**Enolsilylation.** The ketone **100** with a tyrosinol moiety was synthesized by a simple $S_{N2}$ reaction in 78% yield using 2-chloroacetone as the electrophile (eq 13), and 1-phenoxy-2-propanone (**101**) was commercially available.




(13)

**67** **99** **100**

**Scheme XII**




**100** Ar = **67**
**101** Ar = Ph

**102** Ar = **67**
**103** Ar = Ph

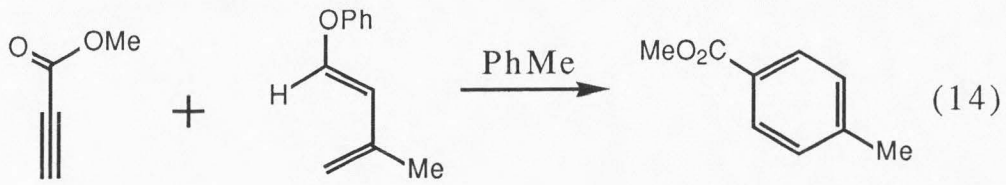
**104** Ar = **67**
**105** Ar = Ph

Trisubstituted dienes **104** and **105** were prepared by a sequence of formylation and enolsilylation of 2-aryloxy-1,3-diketones **102** and **103**, respectively. Thus, the formylation[24] (Scheme XII) of ketone **101** provided diketone **103** in ~70% yield (vacuum distillation). Enolsilylation[22] of diketone **103**, using two equivalents of TMSOTf and triethylamine, generated 1,3-bis[(trimethylsilyl)oxy]-2-phenoxybutadiene (**105**). Purification of 1,3-diketone **102** by use of flash chromatography, rather than vacuum distillation, was not successful, and more research on the purification was needed.

## Synthesis of Diaryl Ethers

**General Studies.** The *trans*-diene **86a** was reacted with methyl propiolate (**107**) in refluxing toluene for 24 h. The phenoxy

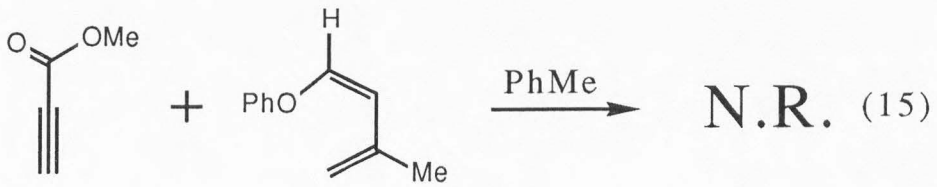
group was eliminated during the thermal reaction to afford the aromatic compound **108** (eq 14).




(14)

**107** **86a** **108**

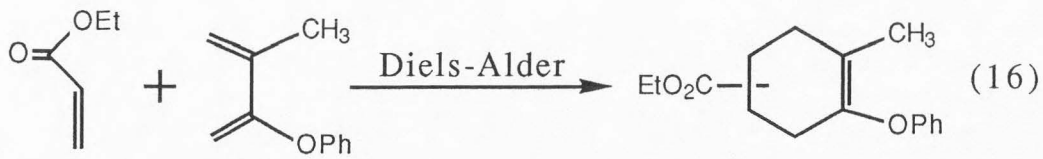
Because the *cis*-isomer **86b** showed no reactivity in the Diels-Alder reaction (eq 15), these two dienes were terminated for any further studies.




(15)

**107** **86b**

2,3-Disubstituted dienes from Figure 4 were used in place of the above dienes for obviating the elimination of the phenoxy group during the cycloaddition. The following reaction was run in a simple model system using 2-methyl-3-phenoxybutadiene (**90b**) and ethyl acrylate (**109**):



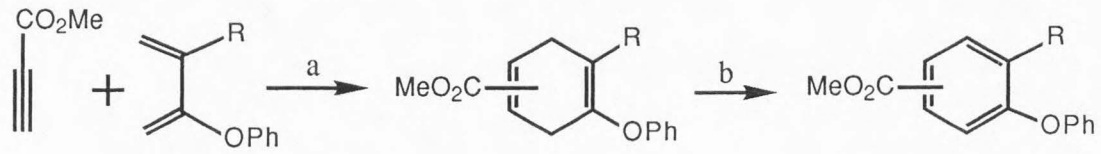

(16)

**109** **90b** **110**

A mixture of two regioisomeric cyclohexenes[25] **110** was obtained in ~40% yield (eq 16). Because this result was encouraging the research was extended to syntheses of diaryl ethers.

**Diaryl Ethers from 2,3-Dioxygenated Dienes.** For the syntheses of less complex diaryl ethers, a simple replacement was made to use alkyne **107** instead of alkene **109** in the cycloaddition reaction (Scheme XIII). Methyl propiolate (**107**) reacted with 2-methyl-3-phenoxybutadiene (**90b**) to generate cyclohexadiene **111a**. Oxidation of the cycloadduct by 1.05 equivalent of DDQ[26] in refluxing benzene resulted in formation of diaryl ether **111b** as an equal mixture of two regioisomers. Diaryl ether **112b** was also generated by use of 2-methoxy-3-phenoxybutadiene (**92b**).

**Scheme XIII**[a]



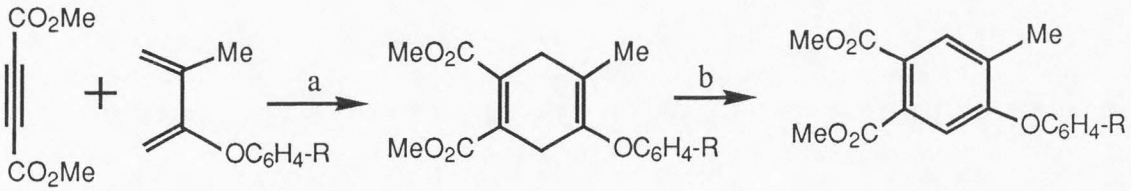

**107** **90b** R = Me **111a** R = Me **111b** R = Me
**92b** R = OMe **112a** R = OMe **112b** R = OMe

[a] (a) toluene, sealed glass tube, 120 °C (oil temperature), 20~30 h, 78%; (b) DDQ, 1.05 eq, benzene, reflux, 2 h, ~100%.

Subsequently, dimethyl acetylenedicarboxylate (**113**) was used to replace methyl propiolate (**107**) in the Diels-Alder reaction. Only one regioisomer, **114b** or **115b,** was possible and was isolated (Scheme XIV). In conclusion, four substituted diphenyl ethers (**111b**, **112b**, **114b** and **115b**) were obtained by oxidation of the

corresponding dienes and fully characterized for demonstrating the capability of the methodology for preparation of diaryl ethers.

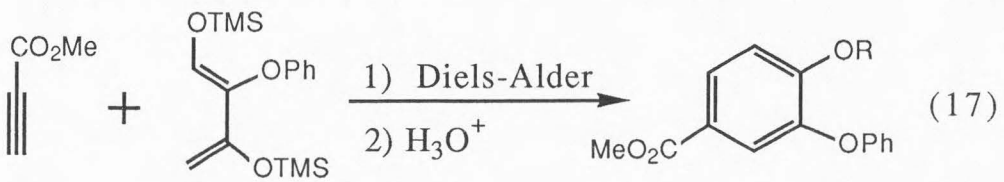
**Scheme XIV**[a]




**113** **90b** R = H **114a** R = H **114b** R = H
**91b** R = p-MeO **115a** R = p-MeO **115b** R = p-MeO

[a] (a) toluene, reflux, 20 h, 95%; (b) DDQ, 1.05 eq, benzene, reflux, 2 h, more than 90%.

**Diaryl Ethers 116 from a 1,2,3-Trioxygenated Diene.** Since the above Diels-Alder reactions were conducted for the construction of diaryl ether bonds without any regioselectivity, a new type of diene with regiocontrolling elements was studied in the Diels-Alder reaction (eq 17).




(17)

**107** **105**

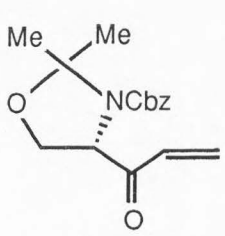
**116** R = H
**117** R = Me

The previously prepared 1,3-bis[(trimethylsilyl)oxy]-2-phenoxybutadiene (**105**) (Scheme XII) was reacted with methyl propiolate (**107**) to generate only one regioisomer **116**. The structure of the substituted phenol **116** was further confirmed by

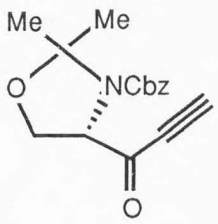
converting it into diaryl ether **117** (MeI, $K_2CO_3$, DMF, overnight), which was identical with one regioisomer of diaryl ether **112b** (Scheme XIII).

## Preparation of Required Dienophiles Derived from L- or D-Serine

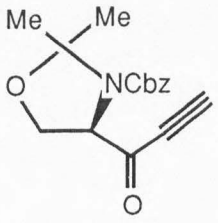
**Chiral Dienophiles.** The use of dienophiles with different functional groups can significantly expand the synthetic utility of this approach. Three dienophiles (**118**, **119** and **120**, Figure 6) were prepared from an optically pure serine moiety. Alkyne **120** proved to be the most useful dienophile in this research.




**118** (S)



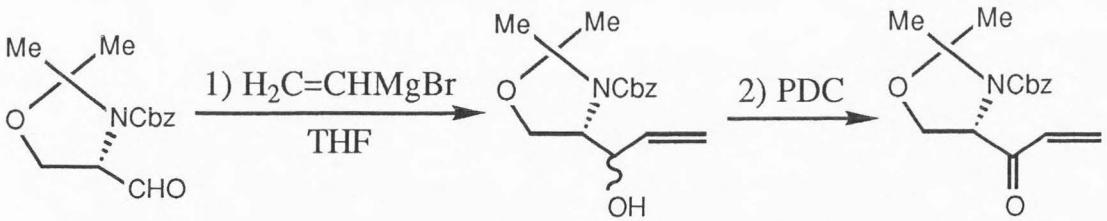

**119** (S)




**120** (R)

**Figure 6.** Structures of required dienophiles for Diels-Alder reactions.

**Scheme XV**

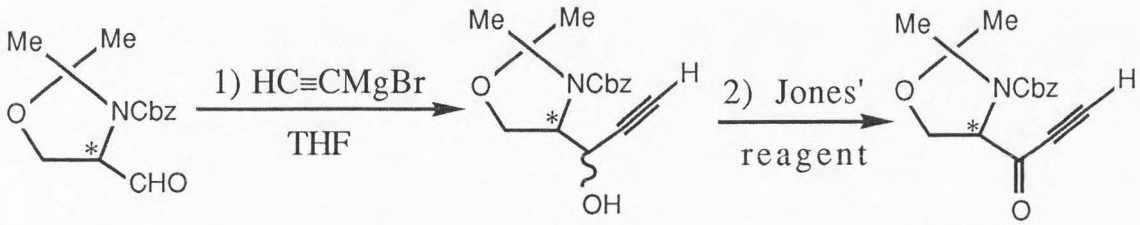



**78b** (S) **121** **118** (S)

**Terminal Enone 118.** Enone **118** was obtained in two steps: (1) addition[27] of vinylmagnesium bromide to the chiral aldehyde

**78b** and (2) oxidation of the obtained alcohol **121** by PDC in $CH_2Cl_2$ at rt. Enone **118**[28] was used only in Diels-Alder model studies (eq 18) because ynone **120** or **119** better served our synthetic purposes.

**Scheme XVI**



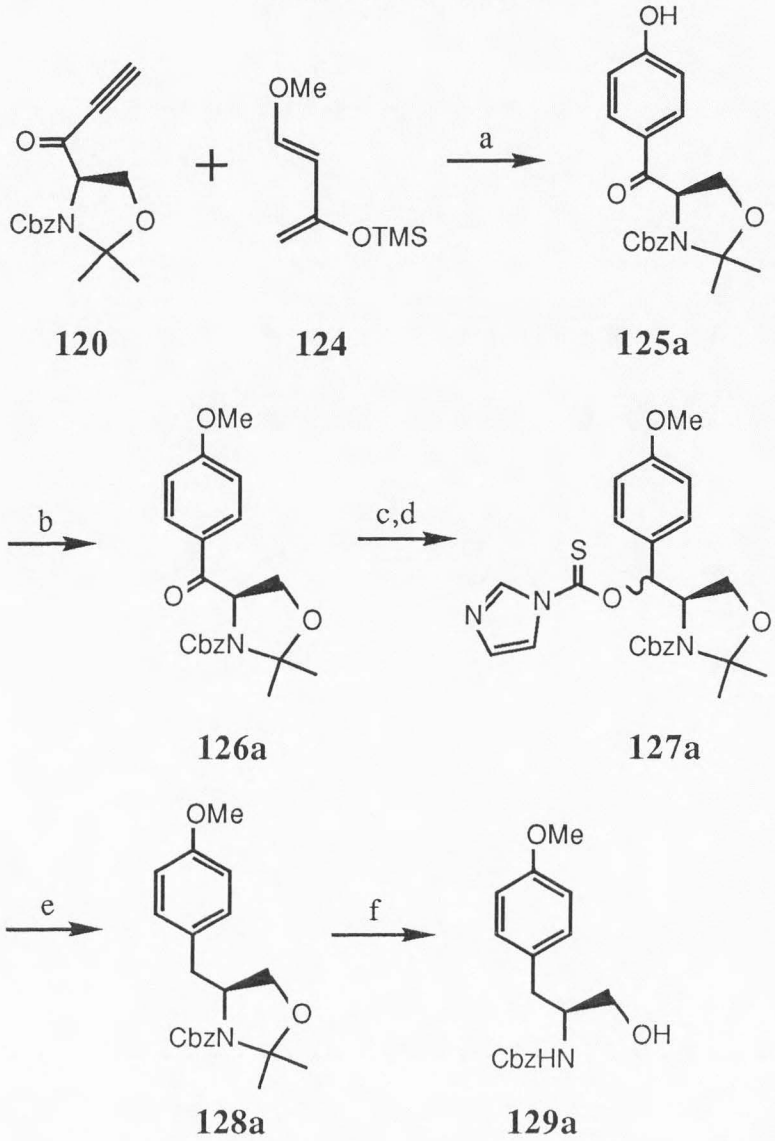

**78a** (R) **122** **120** (R)
**78b** (S) **123** **119** (S)

**Terminal Ynone 120.** The synthetic procedure in Scheme XVI illustrates the preparation of dienophiles **120** and **119**, which were nonracemic terminal ynones with amino acid side chains. The well-known conformationally stable oxazolidine aldehydes **78a** and **78b** served again as the optically pure starting materials. Condensation of aldehyde **78a** with ethynylmagnesium bromide provided a mixture of the diastereomeric alcohols **122**, and subsequent oxidation of the alcohol function in **122** using Jones' reagent,[29] instead of PDC, provided the terminal ynone **120** in ~65% overall yield. The configuration of the ynone can be either R or S, which was obtained from the configuration of the starting aldehyde **78**.

## Enantiospecific Synthesis of the Optically Pure Tyrosinol

**Synthesis of Tyrosinol.** N-Cbz-O-Methyl-L-tyrosinol

**Scheme XVII**[a]




**120** **124** **125a**

**126a** **127a**

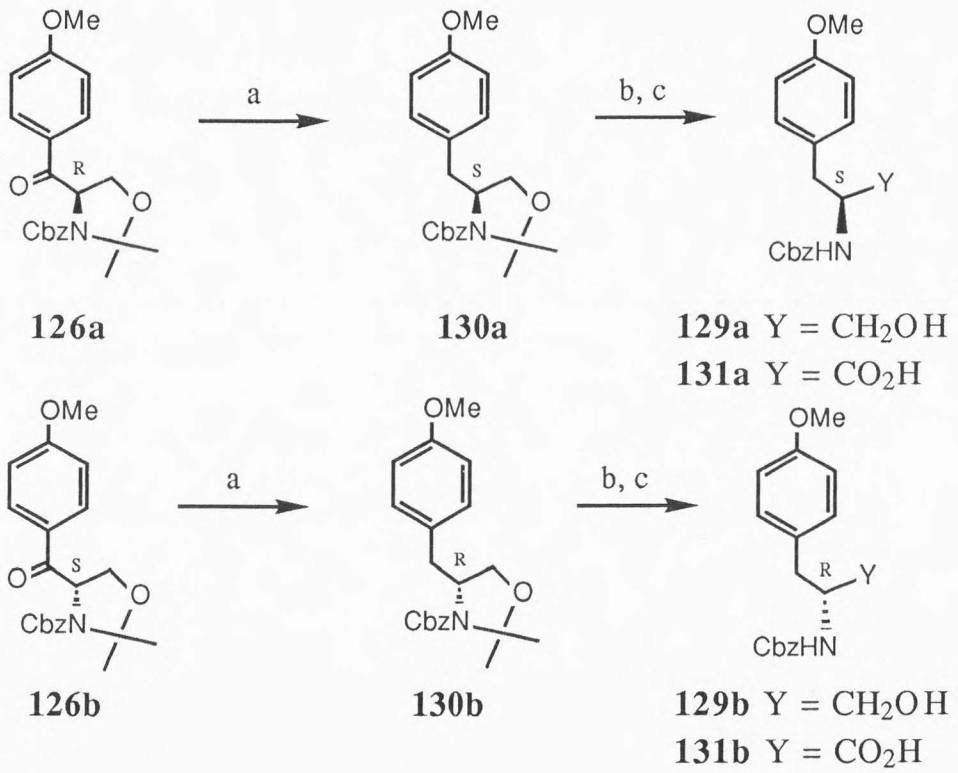
**128a** **129a**

[a] (a) (1) PhMe, reflux, 12 h; (2) THF-$H_3O^+$, 30 min, rt, 85~90 %; (b) MeI, $K_2CO_3$, DMF, rt, 12 h, 82~88%; (c) $NaBH_4$, MeOH, rt, 90%; (d) $S=C(Im)_2$, DMAP, $CH_2Cl_2$, rt, 3 days, 93%; or $ClCH_2CH_2Cl$, reflux, 7 h, 71%; (e) $Bu_3SnH$, AIBN, toluene, reflux, 2 h, 83 %; (f) TsOH, MeOH, rt, 12 h, ~93%.

(**129a**) was prepared from ynone **120**. Condensation of ynone **120** with Danishefsky's diene **124**[30] gave β-keto tyrosinol oxazolidine **125a** in ~88% yield. After O-methylation of the phenolic hydroxy

group of phenol **125a**, two synthetic methods remained for reduction of the keto function in compound **126a** down to the methlyene group: (1) Barton's procedure[31a] (Scheme XVII) and (2) $NaBH_3CN$-$ZnI_2$ combined reagents[31b] (Scheme XVIII). Reduction of the ketone function in **126a** and esterification of the obtained alcohol provided the imidazole thiocarbonyl ester **127a** in 82% overall yield. Removal of the ester in **127a** and methanolysis of the oxazolidine ring gave the N-Cbz-L-tyrosinol (**129a**) in high yield. Tyrosinol **129a** was identical with (NMR and optical rotation) the same compound (tyrosinol **72**) prepared from Cbz-L-tyrosine (**68**).[32]

**Scheme XVIII**[a]

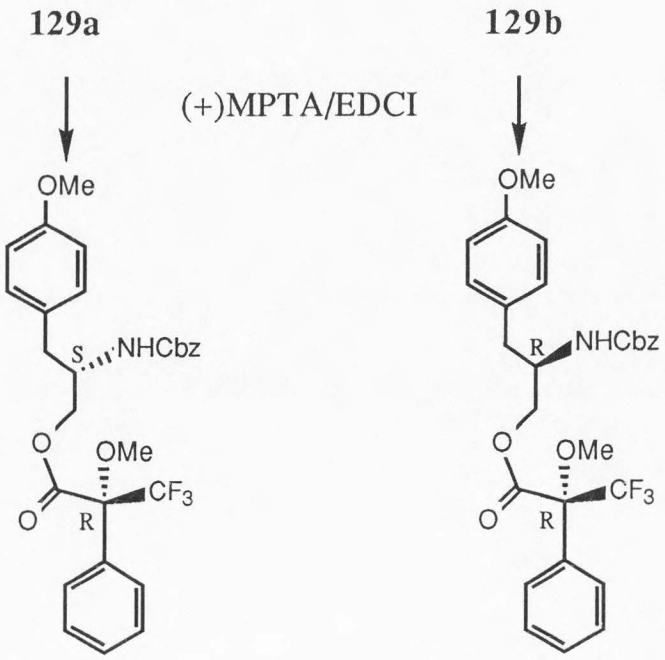



[a] (a) $NaBH_3CN$-$ZnI_2$, $ClCH_2CH_2Cl$, reflux, 12 h, 41~53%; (b) TsOH, MeOH, rt, 12 h, ~93%; (c) ethyl ether, Jones' oxidation, 3 h, 41~61%.

Reduction of the ketone function in **126a** or **126b**, using the $NaBH_3CN$-$ZnI_2$ combined reagents, occurred in ~47% yields. The (S)-configuration of oxazolidine **130a** was derived from (R)-ketone **126a**, and the (R)-configuration of oxazolidine **130b** was derived from (S)-ketone **126b**. Tyrosinol **129a** or **129b** was oxidized into N-Cbz-L-tyrosine (**131a**) or N-Cbz-D-tyrosine (**131b**) using Jones' reagent,[32] respectively. The tyrosinols **130a** and **130b** ($\alpha_D \pm 40^o$) obtained by use of $NaCNBH_3$-$ZnI_2$ seemed to have a lower optical rotation value than the product **128a** ($\alpha_D$ -50°) prepared by use of Barton's procedure. Thus two questions remain: (1) How to determinate the optical purity of the synthetic tyrosinol, in other words, what is the percentage of enantiomeric excess (%ee)? and (2) Does the chiral alkyne **120** racemize during the Diels-Alder reaction?

**Studies of Mosher's Amide of the Synthetic Tyrosinol.** Because the optical value of a compound was not a reliable source for determination of optical purity, finding a proper chemical methodology for the determination of %ee was a practical problem in the research. Application of the well-known method involving the use of Mosher's acid was investigated. The first reaction studied (Scheme XIX) was the esterification of the alcohol functional group in N-Cbz-O-methyl-L-tyrosinol (**129a**) with (R)-(+)-Mosher's acid.[14] Comparing the $^1H$ NMR spectrum of the Mosher's ester of **129a** with that of the other antipode **129b** showed that the chemical shift positions of the α-protons in the two diastereoisomers **132a** and **132b** were distinct. None of the enantiomer was found in the other isomer.

**Scheme XIX**[a]

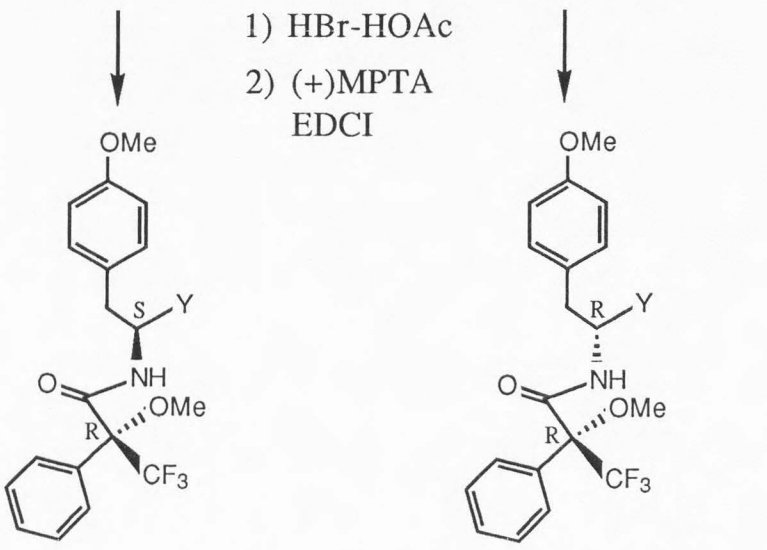



**132a** **132b**

Subsequently, Mosher's amides[33] **133** and **134** were synthesized and used for a better $^1H$ NMR resolution (Scheme XX). In this new system, the (R)-(-)-Mosher's acid was directly connected with the amine functional group in **128a**, α to the chiral center, rather than the alcohol functional group in **129a**, β to the chiral center. A better result was found in that the O-methyl groups of Mosher's acid in the two diastereoisomers **133** and **134** appeared to be located at different positions. The chemical shift of the methyl group was 3.28 ppm for (S,R)-**133**, and 3.32 ppm for (R,R)-**134**. The chemical shift difference between these two peaks was 11.8 Hz. By comparing integrations of the two methoxy peaks in $^1H$ NMR spectra, the sample **128a** ($\alpha_D$ -50°) made using Barton's procedure was tested and showed only one antipode present. The samples **130a** and **130b** ($\alpha_D$ ±40°), made using $NaBH_3CN$-$NaI_2$, showed a diastereomeric

ratio of 15:1, and the samples **74a** ($\alpha_D$ -9°) and **74b**, partially racemized early in this research (p. 22), produced a ratio of 2:1. The conclusion was that no racemization occurred in this synthetic strategy involving the Diels-Alder reaction and subsequent deoxygenation using the Barton procedure.

**Scheme XX**



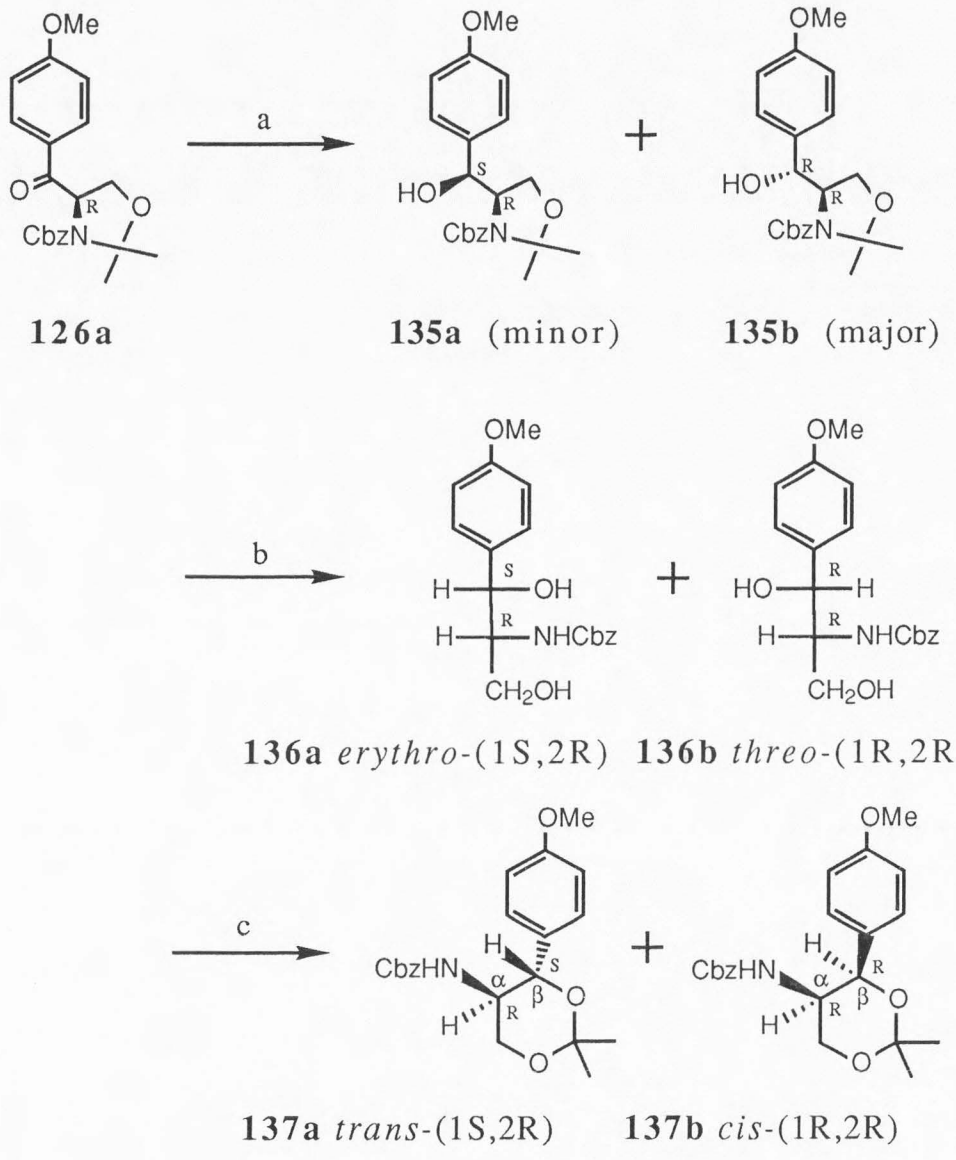

**133** Y = $CH_2OAc$ **134** Y = $CH_2OAc$

## Synthesis of β-Hydroxytyrosinol and Determination of Its Absolute Configuration

Reduction of the ketone function in the optically pure β-keto tyrosinol oxazolidine **126a** using $NaBH_4$ is illustrated. The absolute configuration of the major isomer **135b** was established by conversion to the corresponding dioxane **137b**. Reduction of the ketone in **126a** was performed by reduction with $NaBH_4$ in MeOH at 0 °C for 2 h. Hydrolysis of the resulting mixture **135a** and **135b**

gave diols **136a** and **136b**, which were treated with DMP and tosic acid (Scheme XXI).

**Scheme XXI**[a]




**126a** **135a** (minor) **135b** (major)

**136a** *erythro*-(1S,2R) **136b** *threo*-(1R,2R)

**137a** *trans*-(1S,2R) **137b** *cis*-(1R,2R)

[a] (a) $NaBH_4$, MeOH, O °C, 2 h, 90%; (b) TsOH, MeOH, rt, overnight, 86%; (c) DMP, TsOH, rt, 3 h.

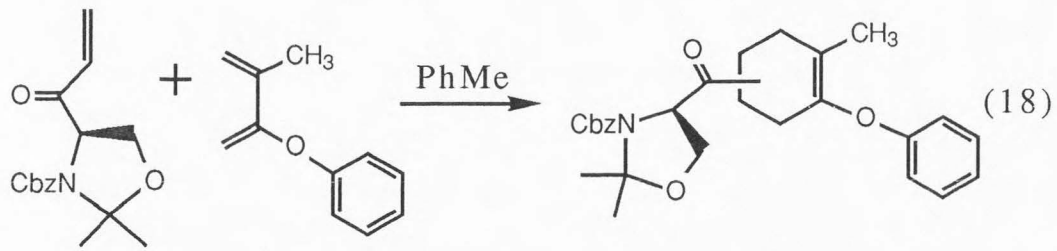
Dioxane **137b** was isolated in ~38% yield. A typical coupling constant of ~1.8 Hz was observed for **137b**, thereby establishing its

*cis*-stereochemistry.[15] Since only *cis*-dioxane **137b** was found in the experiment, the conclusions were that the *threo*-(1R,2R) diol **136b** was the major stereoisomer, and the *erythro*-(1S,2R) diol **136a** the minor stereoisomer.

## Construction of the Fully Differentiated L,L-Isodityrosinol

**Model Studies.** As the formation of less complex diaryl ethers (Scheme XIII and XIV, p. 30) was developed, the following Diels-Alder reactions were run for the model synthesis of L,L-isodityrosinol.

Enone **118** underwent a cycloaddition reaction with 2-methyl-3-phenoxybutadiene (**90b**) (eq 18). The reaction was run at typical cycloaddition conditions (PhMe, reflux). After 24 h, TLC analysis of the reaction mixture clearly indicated that the diene spot was gone, and a new spot was found. The reaction mixture was subjected to MPLC on silica gel using ethyl acetate in hexane as the solvent. Cyclohexene **138**, confirmed by $^1$H NMR as the expected structure,[34] was isolated from the column.

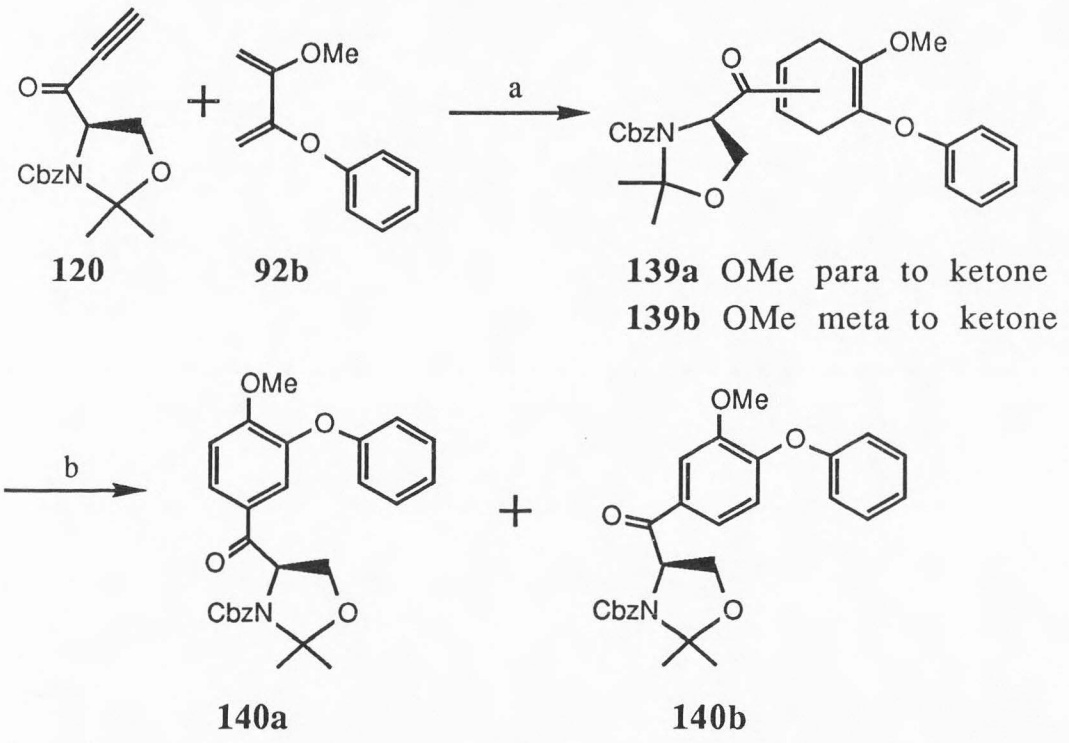



**118** **90b** **138**

Based on the above model synthesis, if terminal alkyne **120** was used instead of the above alkene **118**, the aromatization of the resulting cyclohexadiene **139** would be more easily effected than

that of cyclohexene **138**. The synthetic chemistry[32] of the Diels-Alder reaction in Scheme XXII was realized. Ynone **120** reacted with 2-methoxy-3-phenoxybutadiene (**92b**) in a sealed glass tube for 2 days at 150 °C (oil temperature) and provided two regioisomers **139a** and **139b** in an almost equivalent ratio. Separation of the two regioisomers was achieved by flash chromatography on silica gel. Oxidation of the cyclohexadienes **139a** and **139b** with 1.05 eq of DDQ in boiling benzene generated two optically active diaryl ethers **140a** and **140b**, respectively.

**Scheme XXII**[a]



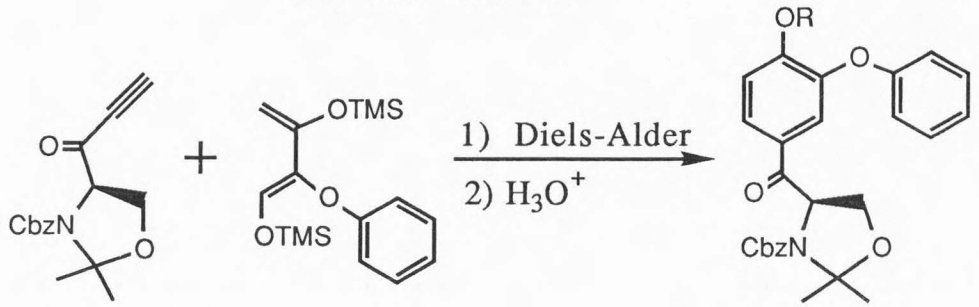

**120** **92b** **139a** OMe para to ketone
**139b** OMe meta to ketone

**140a** **140b**

[a] (a) toluene, sealed glass tube, 150 °C, 2 days, 76% combined yield; (b) 1.2 equiv of DDQ, benzene, reflux, 2~3 h, 80% for **140a**, 75% for **140b**.

The assignment of the regiochemistry[32] of these two regioisomers **140a** and **140b** was made by comparing the $^1H$ NMR spectra of the two regioisomers with that of the known regioisomer **141**, which was isolated from the regiospecific Diels-Alder cycloaddition shown below. 1,3-Bis[(trimethylsilyl)oxy]-2-phenoxy butadiene (**105**) was reacted with alkyne **120** to provide only one regioisomeric diaryl ether **141** in ~49% yield.[32] O-Methylation (MeI, $K_2CO_3$, DMF, overnight) of diaryl ether **141** provided methyl ether **142**, which was identified as regioisomer **140a**. Both products from Scheme XXII and those from Scheme XXIII were optically active compounds.

**Scheme XXIII**

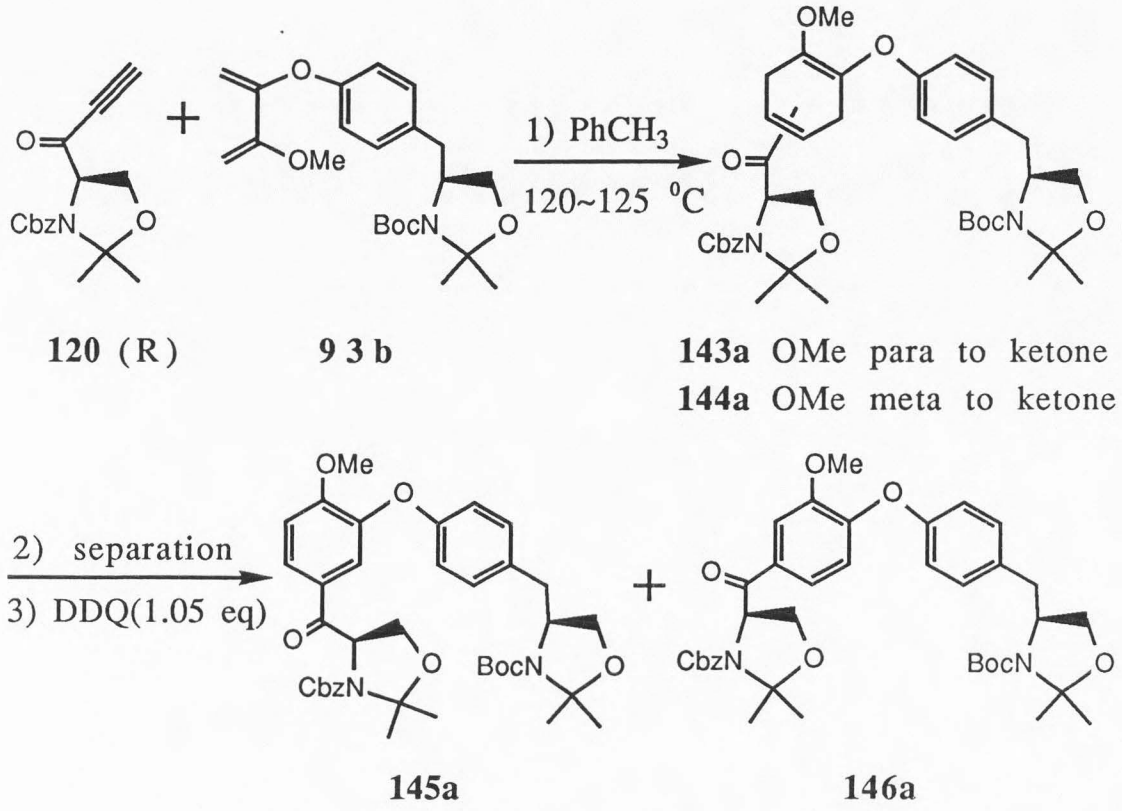



**120** **105** **141** R = H, **142** R = Me

**Construction of a Precursor to (L,L)-Isodityrosinol.** After the above preliminary syntheses, the preparation of (L,L)-isodityrosinol **149a** was the next goal. A key precursor **145a** to (L,L)-isodityrosinol **149a** was generated from the cycloaddition in Scheme XXIV. Condensation of ynone **120** with 2,3-bisoxygenated diene **93b** at lower temperature[32] (120 °C) provided **143a** and **144a** (ratio = 1:1) in ~91% yield. Separation of cyclohexadiene **143a** from **144a** was achieved by MPLC on silica gel using 30% ethyl

acetate in hexane. Oxidation of each using DDQ provided the key precursor **145a** and the other regioisomer **146a**, respectively.

**Scheme XXIV**

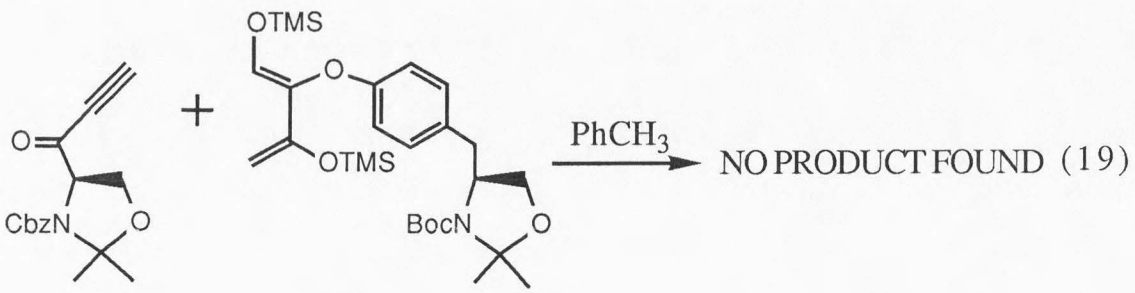



**120** (R) **93b** **143a** OMe para to ketone
**144a** OMe meta to ketone

**145a** **146a**

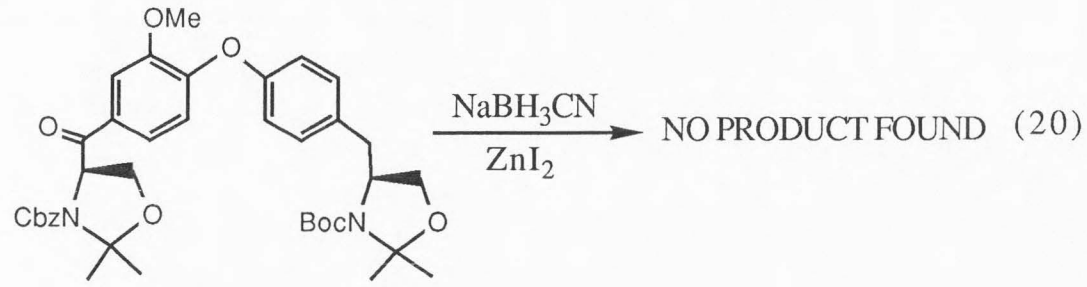
The assignments of these two regioisomers were confirmed by comparing the aromatic region of the $^1H$ NMR spectra to the spectrum of the known regioisomer **142**, where the phenoxy group was present rather than the tyrosinol moiety. Isomer **146a** was also a useful chiral starting material for these model studies. Both epimers **145b** and **146b** (ratio = 1:1) with (S,S)-configuration were also synthesized by use of alkyne **119** of (S)-configuration in a similar manner.

1,2,3-Trioxygenated diene **104** (Scheme XII, p. 28), rather than 2,3-bisoxygenated diene **93b**, was examined in the regiospecific Diels-Alder reaction (eq 19). Surprisingly, there were no products isolated from the reaction, which may be due to the unpurified nature of the diene **104** or its precursor diketone **102.**




**120** **104**

**Reduction of the Ketone Functional Group in 145a.** The reduction of the ketone functional group in **145a** and **146a** to a methylene group was studied. Two methodologies[31a,31b] were examined in this research. Isomer **146a** was taken as a chiral starting material for the following one-step reduction.

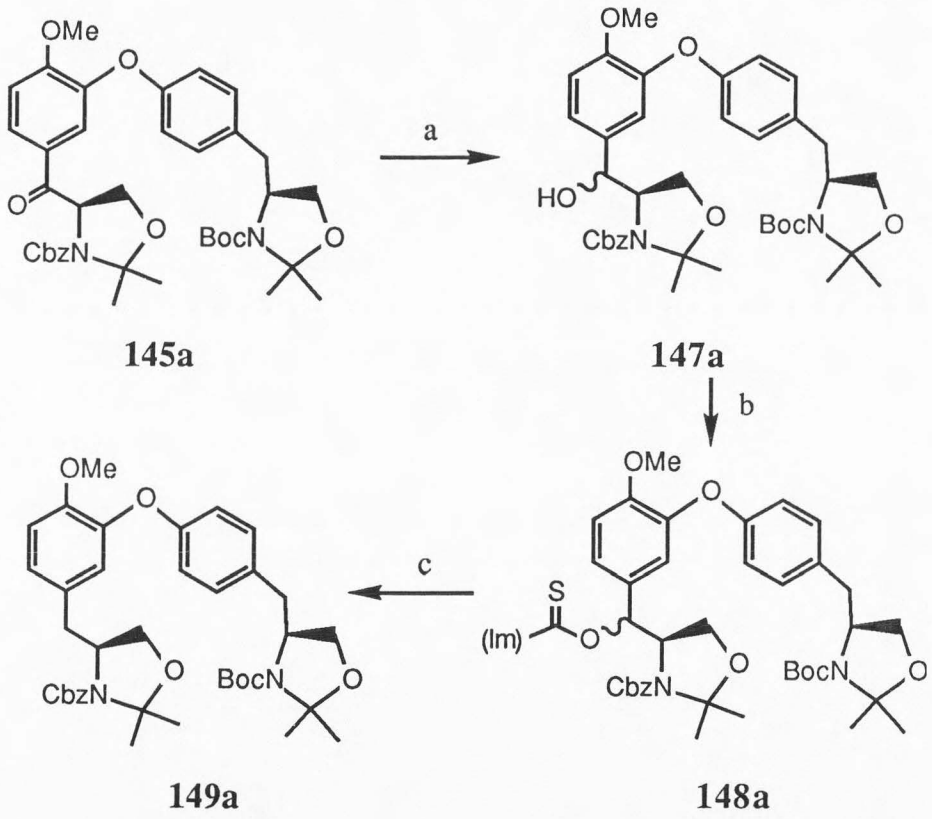



**146a**

As no expected product was isolated from the above one-step reduction[31b] using $NaBH_3CN/ZnI_2$ combined reagent (eq 20), a three-step procedure based on Barton's method[31a,35] was developed to reduce the ketone functional group in **145a**. Thus, reduction of

ketone **145** (Scheme XXV) was carried out by $NaBH_4$ in MeOH at rt or 0 °C to provide a mixture of diastereomers. The esterification of the alcohol in **147a** with thiocarbonyl diimidazole and Barton's reduction of the resulting ester **148a** provided the final isodityrosinol **149a**. The synthesis of isodityrosinol **149a** with two oxazolidine rings was accomplished, but two research problems remained: (1) to determine the diastereomeric purity of the isodityrosinol; (2) to differentiate the two oxazolidine rings, since an undifferentiated isodityrosinol would dramatically decrease the synthetic utility of the research.

**Scheme XXV**[a]

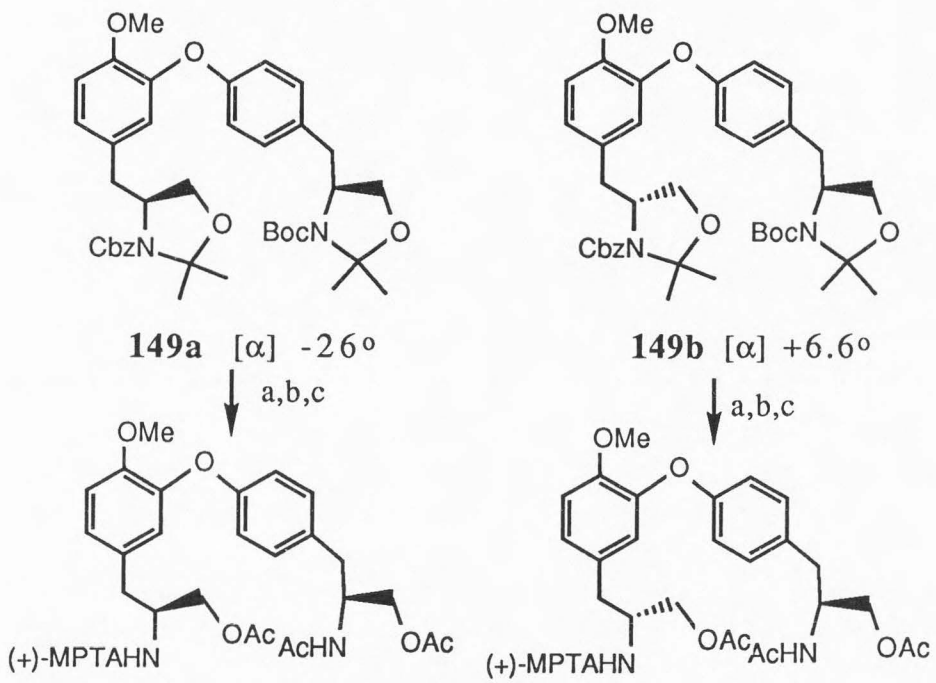



**145a** **147a** **148a** **149a**

[a] (a) $NaBH_4$, O °C, 2 h, 93%; (b) $(Im)_2C=S$, DMAP, $ClCH_2CH_2Cl$, reflux, 7~12 h, 73%; (c) $Bu_3SnH$, AIBN, toluene, reflux, 2 h, 85%.

**Mosher's Amide Studies of the Synthetic Isodityrosinol.** Even though alkyne **120** seemed configurationally stable to the reaction conditions for the synthesis of optically pure tyrosinol, a chemical methodology involving Mosher's acid was used to determine the diastereomeric purity of the synthetic L,L-isodityrosinol **149a**. The (R,S)-diastereomer **149b** was prepared by use of ynone **119** instead of **120**.

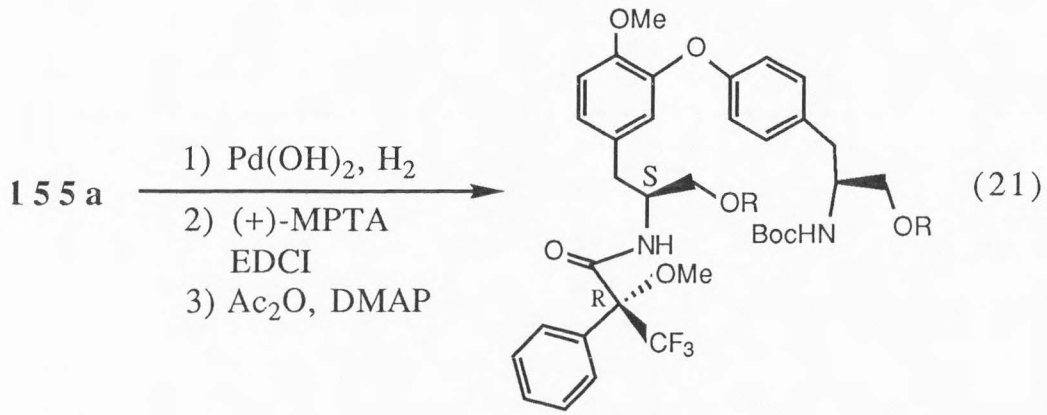
**Scheme XXVI**[a]




[a] (a) $CF_3CO_2H$, $CH_2Cl_2$; (b) 6 equiv $Ac_2O$, DMAP, 20% pyridine in $CH_2Cl_2$; (c) (1) HBr in HOAc, (2) (R)-(+)-Mosher' acid, $Et_3N$, HOBt, EDCI, $CH_2Cl_2$.

Fortunately, the chemical shift ($\delta$ = 3.28 ppm) of the methoxy group of Mosher's acid in diastereomer **150a** was different from that ($\delta$ = 3.32 ppm) in diastereomer **150b**. $^1$H NMR spectrum of an admixture of **151a** and **150b** clearly indicated the resolution of the diastereotopic O-methyl peaks of the Mosher's amides. The presence of the other diastereomer was not observed in each diastereomer.

Diol **155a**, prepared as shown in Scheme XXVII, was also tested by the same methodology. Removal of the Cbz protecting group in diol **155a** by use of $Pd(OH)_2/H_2$ was successful. Acylation of the amino group with Mosher's acid generated amide **151**, and acetylation of the two alcohol functions in **151** furnished **152**. As expected, the chemical shift for the methoxy proton of Mosher's acid in **151** was 3.27 ppm and for **152** 3.29 ppm. Consistent with the above results, there was no other epimeric peak corresponding to the (R,S) configuration found in this (S,S)-diastereomer.



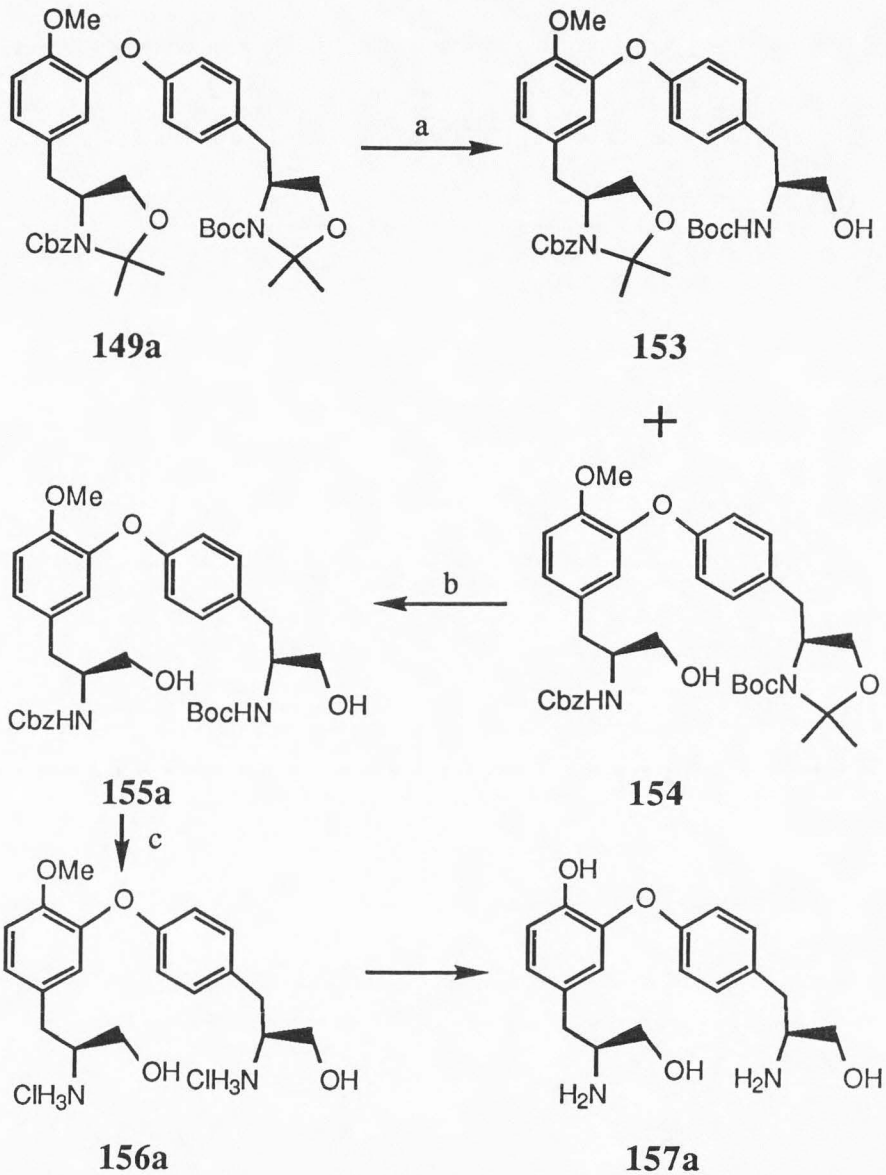

(21)

**151** R = H, **152** R = OAc

**(L,L)-Isodityrosinol in a Fully Differentiated Form.** Oxidation of the two alcohol functional groups in diol **155a** (Scheme XXVII) was the early research plan. The dicarboxylic acid obtained

from the oxidation stage could be esterificated with $CH_2N_2$. The diester, if obtained, would be a formerly synthesized compound, which had been made by Boger's research group.

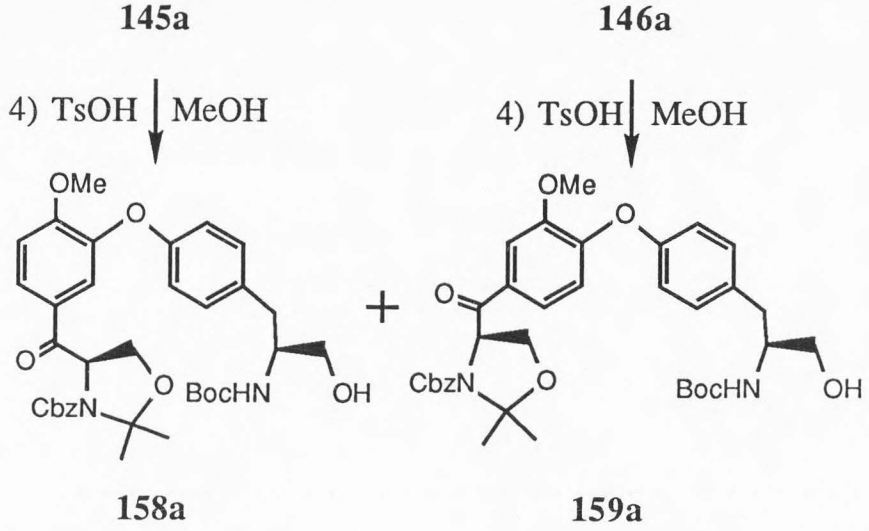
**Scheme XXVII**[a]




[a] (a) TsOH, MeOH, rt, 4 h; (b) TsOH, MeOH, rt, over night, (c) 6 N HCl.

Because a mixture of **153** and **154** was isolated and diol **155a** was obtained in low yield (~25%), the above plans for the oxidation of diol **155a** and for the synthesis of isodityrosinol **157a** proved unpromising. Treatment of **149a** with mild acid (TsOH), however, gave a mixture of monoalcohols (**153** and **154**) in a 4:1 ratio, thus indicating that methanolysis of the two oxazolidine rings was occurring at different rates.

**Scheme XXVIII**[a]

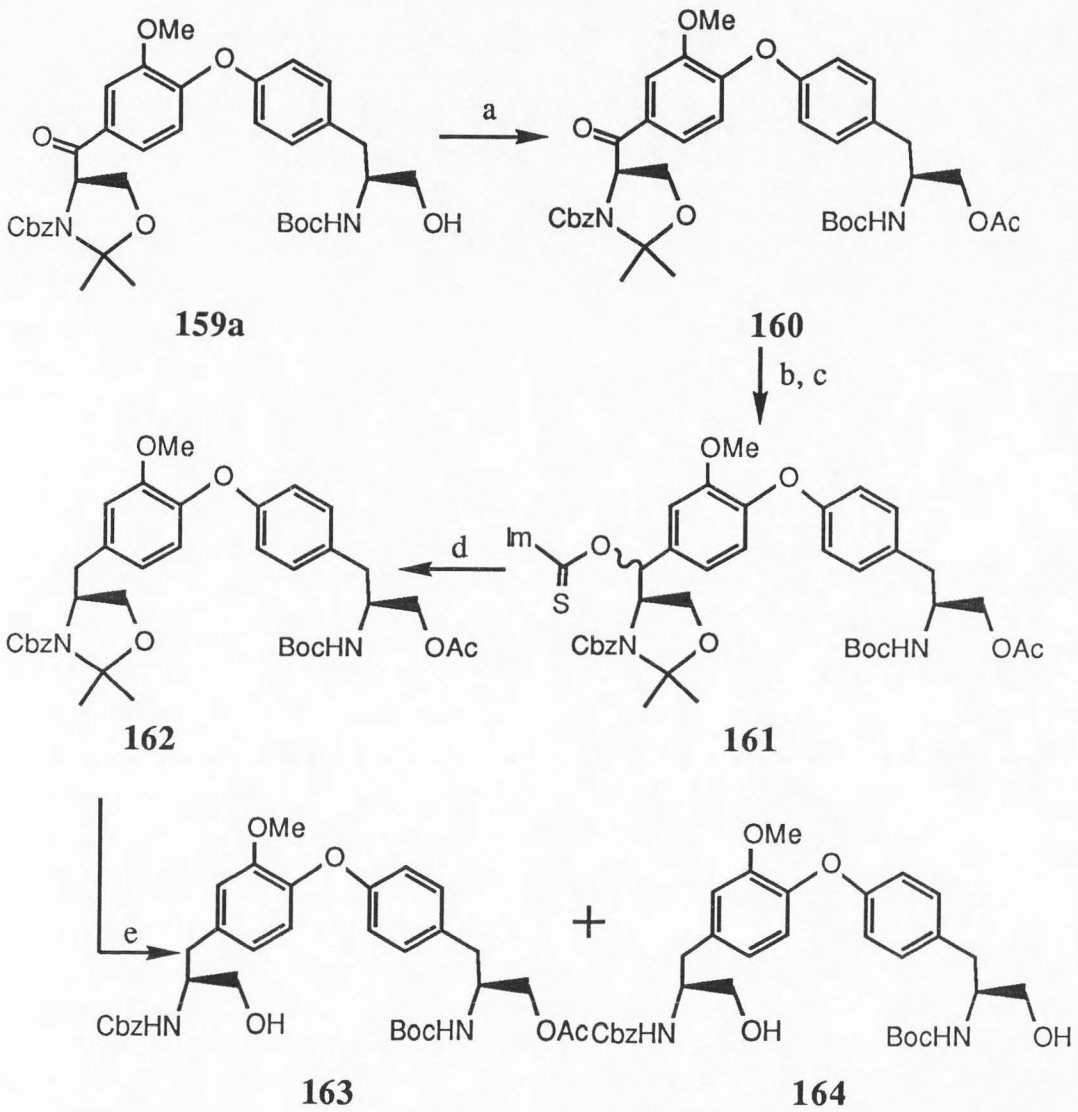



**158a** **159a**

Following this observation, two methanolysis reactions were run in methanol containing TsOH for 2-3 h (Scheme XXVIII) using the previously described ketones **145a** and **146a**. A fortuitous selective methanolysis of one of the oxazolidine rings in **145a** or **146a** was observed. Yields (68 to 78%) of monoalcohols **158a** and **159a** depended on the reaction time and the work-up procedure. The structures of **158a** and **159a** were clearly confirmed by $^1H$ NMR. The tyrosinol methylene hydrogens occurred as a doublet in

**158a** or **159a**, rather than as an ABX pattern observed in the precursor **145a** or **146a**, respectively. The detailed chemistry was published as a communication.[36]

**Scheme XXIX**[a]



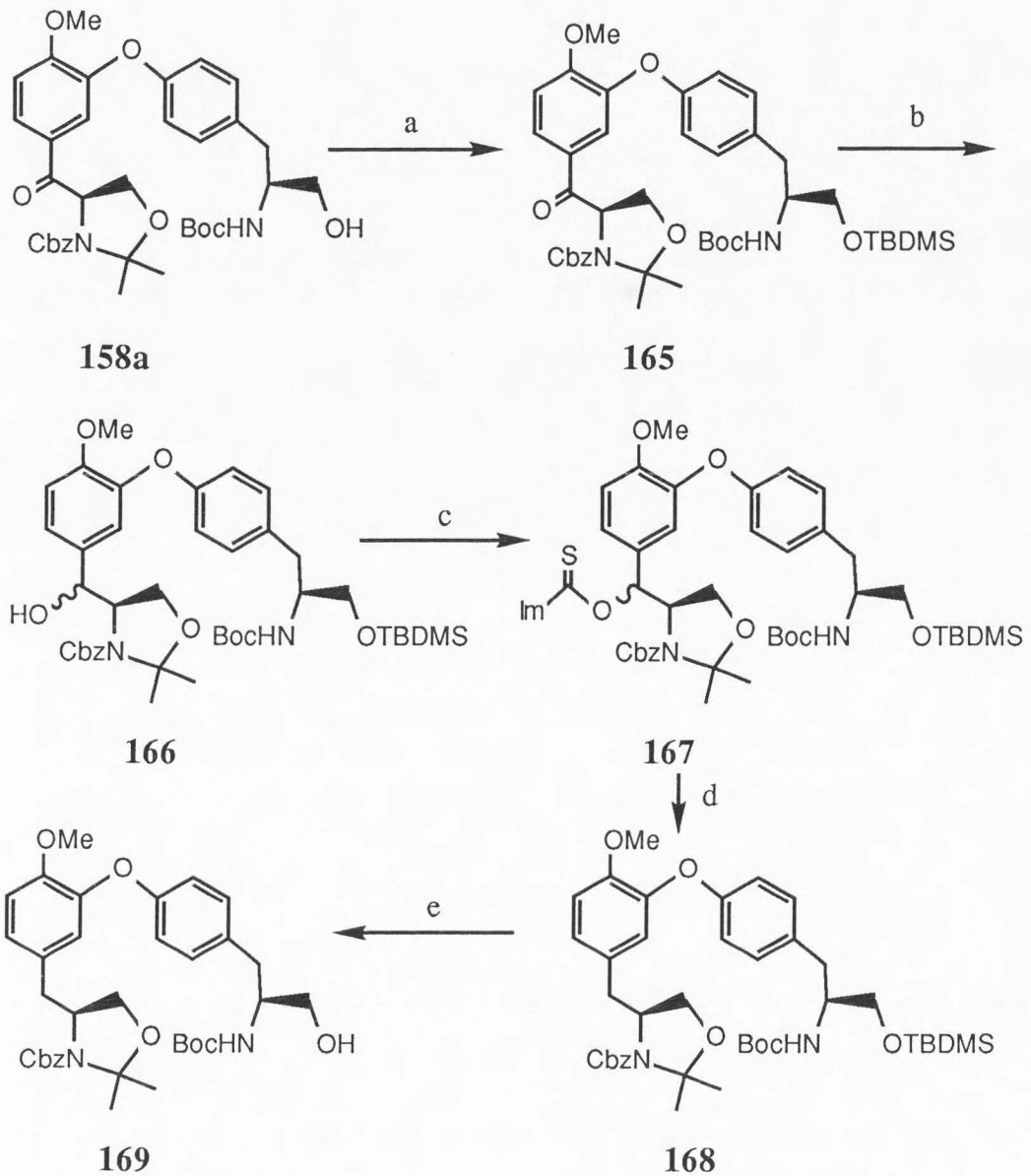

**159a** **160** **162** **161** **163** **164**

[a] (a) $Ac_2O$, 20% pyridine in $CH_2Cl_2$; (b) $NaBH_4$, MeOH, O °C, 2 h, 60~90%; (c) $(Im)_2C{=}S$, DMAP, $CH_2Cl_2$, rt, 3 days, 93%; (d) $Bu_3SnH$, AIBN, toluene, reflux, 73%; (e) TsOH, MeOH.

Selecting a suitable protecting group for the alcohol functional group in monoalcohol **158a** or **159a** depended on the further synthetic applications of these chiral materials. The para-isomer **159a** was used as a model for selecting a proper protecting group (Scheme XXIX). Monoalcohol **159a** was protected by reaction with $Ac_2O$[37a] to provide ester **160**. Reduction of the ketone in **160** with $NaBH_4$ provided the benzyl alcohol, which was converted into imidazole thiocarbonyl ester **161** in 93% yield. Isodityrosinol **162**[37b] was obtained by Barton's reduction in 73% yield, but a mixture of alcohols **163** and **164** was generated in the next methanolysis step. Further use of the acetyl protecting group was terminated because variable yields of the benzyl alcohol due to the partial reduction of acetyl group by $NaBH_4$ were also obtained.

The *tert*-butyldimethylsilyl (TBDMS)[38] protecting group was introduced into this research after this unsuccessful procedure. A five-step synthesis was developed in Scheme XXX for synthesis of the fully differentiated isodityrosinol **169**, which is a suitable precursor for synthesis of isodityrosine peptide antibiotics.[36] The alcohol in **158a** was protected by reaction with TBDMSCl in 100% yield. Reduction of the ketone with $NaBH_4$ provided the benzyl alcohol **166**, which furnished ether **168** in good yield after deoxygenation via Barton's procedure.[35] After deprotection of the alcohol in **168**, the monoalcohol **169** was obtained in 100% yield. The diastereomerical purity of the alcohol was probed by the chemical methodology (Scheme XXVI) used earlier in this laboratory. The satisfactory results of the Mosher's amide studies of isodityrosinol **169** have been published.[36]

**Scheme XXX**[a]



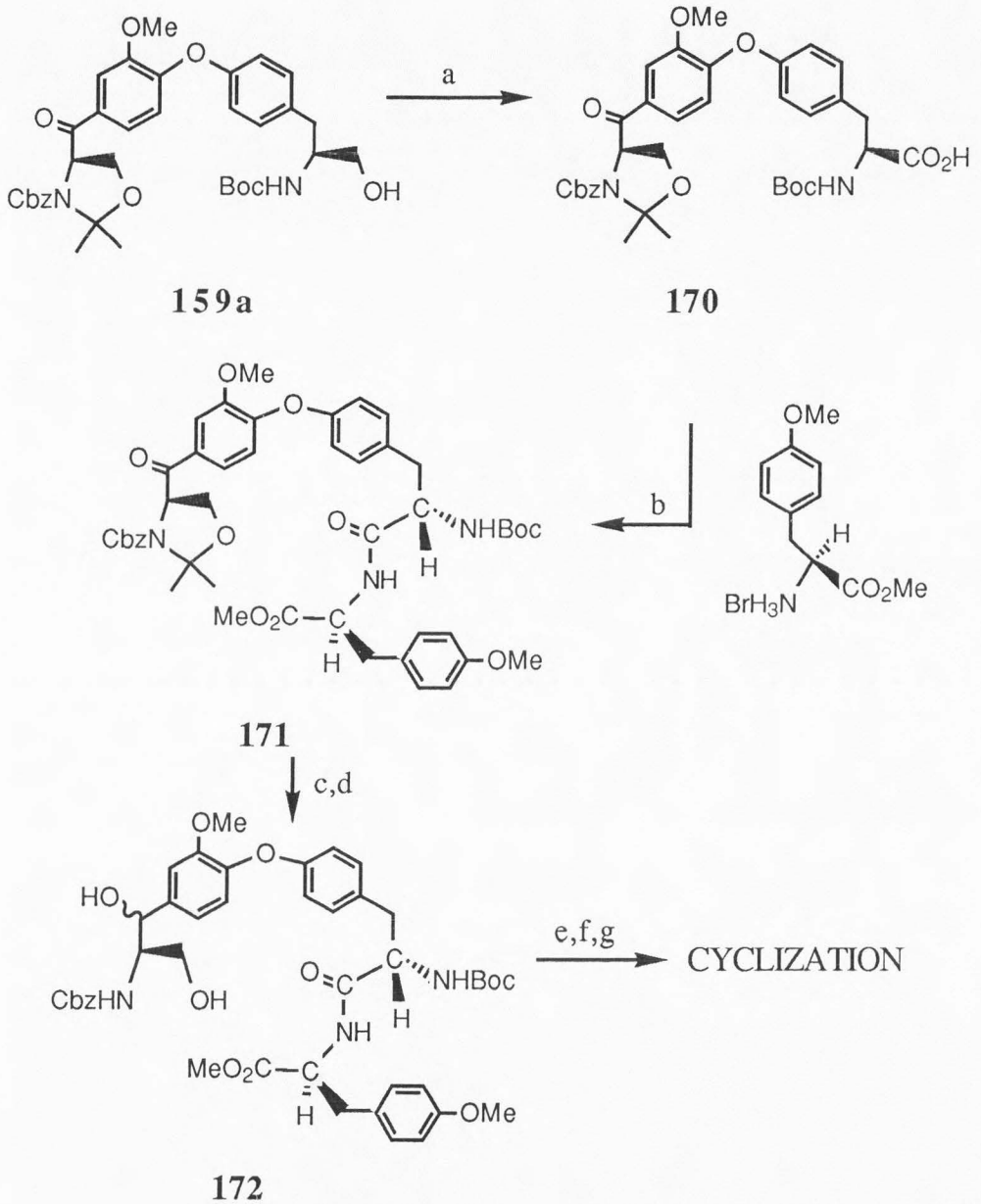

[a] (a) TBDMSCl, TEA, $CH_2Cl_2$, rt, overnight, 100%; (b) $NaBH_4$, MeOH, O °C, 2~3 h, 95%; (c) $S=C(Im)_2$, DMAP, $ClCH_2CH_2Cl$, reflux, 63%; (d) $Bu_3SnH$, AIBN, toluene, reflux, 2~3 h, 96%; (e) $Bu_4NF$, THF, rt, 1 h, 100%.

## A New Synthetic Approach to Isodityrosine-derived Agents K-13 and OF4949-III

**Model Studies for Synthesis of K-13.** Since the fully

differentiated (L,L)-isodityrosinol **169** was obtained in good yield, a model synthesis for K-13 using the para-regioisomer **159a** is illustrated in Scheme XXXI. Cyclization of the para-isomer would then yield a new family of regioisomeric isodityrosine antibiotics.

**Scheme XXXI**[a]



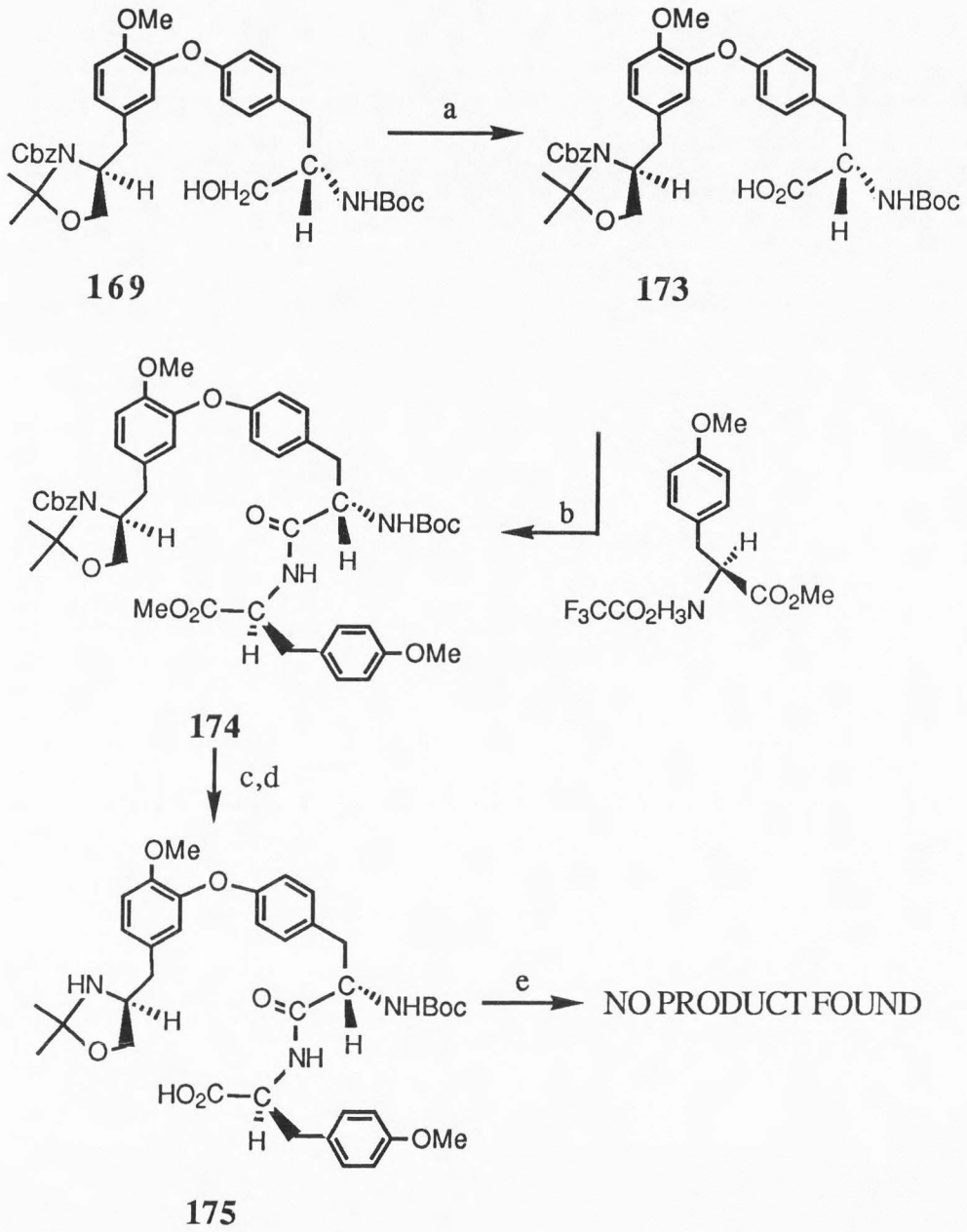
(a) $NaIO_4$, $RuCl_3$, $MeCN/CCl_4/H_2O$, 0 °C, 2~3 h, 78%; (b) O-methyl-(L)-tyrosine methyl ester, $Et_3N$, HOBt, EDCI, $CH_2Cl_2$, 0~25 °C, 12 h, 72%; (c) $NaBH_4$, MeOH, 0 °C, 2~3 h, quantitative yield; (d) TsOH, MeOH, rt, 8 h, 70%; (e) LiOH, $THF/MeOH/H_2O$, rt, 4 h, 75%; (g) $Pd(OH)_2$, $H_2$, 12 h, quantitative yield; (f) 1.5 equiv of DPPA, 4.0 equiv of $NaHCO_3$, DMF (0.006 M), 0 °C for 12 h, rt for 60 h, 0%.

Thus, monoacid **170** was obtained by oxidation of the primary alcohol in **159a**, using $NaIO_4$ and $RuCl_3$,[39] and subsequently coupled with O-methyl-L-tyrosine methyl ester to provide **171** in 52% overall yield. After a sequence of reduction of the ketone, methanolysis of the oxazolidine ring in **171**, tripeptide **172** was characterized by $^1H$ NMR and elemental analysis. Hydrolysis of the methyl ester and removal of Cbz group in **172** resulted the corresponding linear amino acid in high yield. Cyclization of the amino acid was attempted. TLC analysis of the reaction mixture indicated that no neutral cyclic product was formed.

**K-13.** The alcohol function in the fully differentiated isodityrosinol **169** was oxidized using $NaIO_4$ and $RuCl_3$,[39] and the resulting acid **173** was then coupled with O-methyl-L-tyrosine methyl ester under standard conditions to provide the linear tripeptide **174** in modest yield (56%). Hydrolysis of the methyl ester and removal of Cbz group in **174** were effected using LiOH and $Pd(OH)_2$, respectively. Cyclization of the resulting tripeptide **175** was also attempted. Unlike the above result, a small amount of neutral cyclic product was isolated. $^1H$ NMR analysis of the product indicated some unexpected peaks in the up-field region, which may be due to an N-isopropyl group formed by reduction of a Schiff base

(imine) after removal of the Cbz group in the hydrogenation reduction. More research on this cyclization is needed.

**Scheme XXXII**[a]

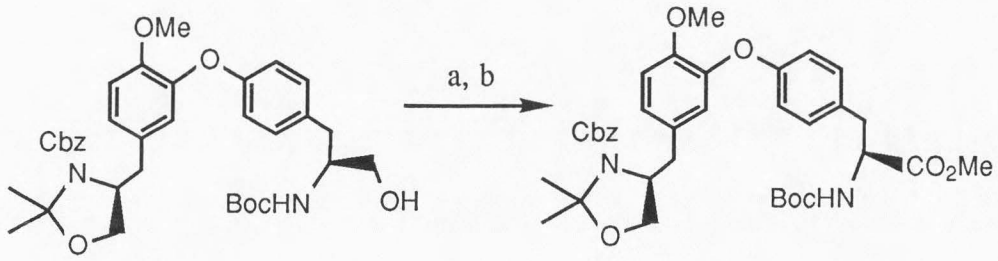



**169** **173** **174** **175**

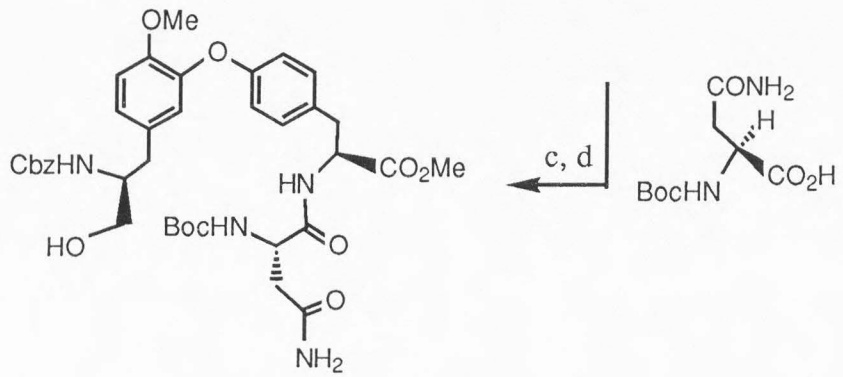
[a] (a) $NaIO_4$, $RuCl_3$, $MeCN/CCl_4/H_2O$, 0 °C, 2~3 h, 78%; (b) O-methyl-L-tyrosine methyl ester, $Et_3N$, HOBt, EDCI, $CH_2Cl_2$, 0~25 °C, 12 h, 51%; (c) LiOH, $THF/MeOH/H_2O$, rt, 4 h, 75%; (d) $Pd(OH)_2$, $H_2$, 12 h,

100% yield; (e) 1.5 equiv of DPPA, 4.0 equiv of $NaHCO_3$, DMF (0.006 M), 0 °C for 12 h, rt for 60 h, low yield.

**Scheme XXXIII**[a]




**169** **176**




**177**

[a] (a) $NaIO_4$, $RuCl_3$, $MeCN/CCl_4/H_2O$, 0 °C, 2~3 h, 78%; (b) $CH_2N_2$, ethyl ether, 0 °C; (c) $CF_3CO_2H$, $CH_2Cl_2$, rt, 30 min; (d) N-Boc-asparagine, $Et_3N$, HOBt, EDCI, $CH_2Cl_2$, 0~25 °C, 12 h, 51%.

**OF4949-III.** Synthesis of OF4949-III (**3**) was also investigated (Scheme XXXIII). Oxidation of the alcohol function in the fully differentiated isodityrosinol **169**, using the $RuCl_3$ and $NaIO_4$ combined reagents, occurred in 78% yield; the resulting acid was quenched with $CH_2N_2$ to provide the methyl ester **176** in high yield. Removal of the Boc group and hydrolysis of the oxazolidine ring in **176** were effected by treatment with $CF_3CO_2H$ at rt for 30 min. The

linear tripeptide **177** was obtained in 51% yield by coupling the resulting amino methyl ester with N-Boc-L-asparagine. Oxidation of the alcohol in **177** and cyclization of the resulting tripeptide were not attempted since only a small amount of tripeptide **177** was obtained.

## SUMMARY AND CONCLUSION

Construction of both simple diaryl ethers and L,L-isodityrosinol in a fully differentiated form was achieved by application of the Diels-Alder cycloaddition reaction. The required aryloxy dienes for the cycloaddition were prepared by using (a) the Wittig reaction, (b) Tebbe's reagent or a modified titanium reagent and (c) an enolsilylation. Synthesis and characterization of less complex diaryl ethers were accomplished by a sequence of cycloaddition (toluene, reflux) and aromatization (DDQ). A regiospecfic Diels-Alder reaction using a 1,2,3-trioxygenated diene was also studied.

For syntheses of tyrosinol and β-hydroxytyrosinol, a acetylenic ketone **119** or **120**, derived from optically pure L-serine or D-serine, was synthsized. Cycloaddition of the acetylenic ketone with Danishefsky's diene, along with and reduction of the ketone function in the adduct by use of $NaBH_4$, gave β-hydroxytyrosinol in high yield. Deoxygenation of the secondary alcohol in the β-hydroxytyrosinol, via Barton's procedure or the $NaCNBH_3/ZnI_2$ combined reagent, provided optically active tyrosinol. Tyrosinol samples obtained from both the Diels-Alder reaction and commercial tyrosine were investigated by $^1H$ NMR spectra of the corresponding Mosher's amides. The results of the Mosher's acid studies showed that no racemization occurred in the above strategy involving the Diels-Alder reaction and subsequent deoxygenation by using the Barton's procedure.

A novel synthetic strategy for preparation of L,L-isodityrosinol **169** in a fully differentiated form was developed. Condensation of

the alkyne **120** and the aryloxy diene **93b**, derived for N-Cbz-L-tyrosine, provided two regioisomers in high yield. Aromatization of the required cyclohexadiene adduct and reduction of the ketone function in the resulting diaryl ether gave the final L,L-isodityrosinol **169** in 37% overall yield (based on the Diels-Alder adduct). The two alcohol groups and two amine functional groups of L,L-isodityrosinol **169** were in different protected forms. The diastereomeric purity of the synthetic L,L-isodityrosinol was also proved by $^1$H NMR spectra studies of the corresponding Mosher's amide.

Finally, synthetic studies of isodityrosine-derived agents K-13 and OF4949-III were also attempted. Syntheses of the tripeptide precursors to K-13 and OF4949-III were achieved by coupling the monoacid, derived from the oxidation of the primary alcohol in the synthetic L,L-isodityrosinol, with the corresponding L-tyrosine and L-asparagine, respectively. Cyclizations of the resulting amino acids were unsuccessful.

## EXPERIMENTAL SECTION

Infrared spectra of samples were obtained on a Perkin-Elmer 1750 FT-IR. Samples were run as neat (film) or as $CHCl_3$ solution using NaCl solution cells. $^1H$ NMR spectra were recorded at 300 MHz (Varian XL-300 NMR) or 270 MHz (JEOL JNM-GSX270). $^{13}C$ NMR were measured at 75.44 MHz or 67.90 MHz using $CDCl_3$ as solvent. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ 85018. All solvents were redistilled using standard techniques when necessary. Most reagents were purchased from Aldrich Chemical Company or Sigma Company.

**N-Dimethylethyloxycarbonyl-(S)-tyrosinol (66).** To a stirred solution of N-Boc-L-tyrosine (**65**) (1.40 g, 5.0 mmol) in 60 mL of anhyd ethyl ether was added LAH (0.38 g, 10 mmol). The mixture was heated at reflux for 3 h, then cooled to rt, quenched with 1 N HCl and diluted with ethyl ether. The ether layer was washed with saturated $NaHCO_3$, then brine, and dried over $MgSO_4$. Evaporation in vacuo gave 1.10 g (82% yield) of the protected alcohol **66** as a white foam; this material could be used as obtained in the next reaction. An analytical sample was purified on flash chromatography on silica gel with 15% acetone in chloroform as eluent: $[\alpha]_D$ -23° (c 0.82, MeOH); IR (film) 3400, 2932, 1681, 1615, 1597, 1515, 1455, 1246, 1107, 957, 845 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.74 and 7.15 ($A_2B_2$ doublets, 4 H), 4.80-4.82 (br m, 1 H), 3.80-3.82 (br m, 1 H), 3.65 (dd, 1 H, $J$ = 11.1, 3.8 Hz), 3.52 (dd, 1 H, $J$ = 11.1, 5.5 Hz), 2.74 (d, 2 H, $J$ = 7.1 Hz), 1.42 (s, 9 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 156.59, 154.85, 130.28, 129.00, 115.51, 80.12, 63.83, 53.87, 36.60, 28.32.

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.89; H, 7.93; N, 5.24. Found: C, 62.90; H, 7.95; N, 4.99.

**(4S)-3-(*t*-Butyloxycarbonyl)-2,2-dimethyl-4-(p-hydroxyphenylmethyl)oxazolidine (67).** To a solution of N-Boc-(S)-tyrosinol (**66**) (1.10 g, mmol) in 80 mL of acetone was added TsOH (0.30 g), DMP(15 mL), and the mixture was stirred at rt overnight. The solvent was removed in vacuo and the residue taken up in 100 mL of EtOAc and 20 mL of water. The separated organic layer was washed with saturated $NaHCO_3$, brine, and dried over anhyd $MgSO_4$. After the solvent was removed in vacuo, the product was purified by flash chromatography on silica gel with 20% ethyl acetate in hexane to provide oxazolidine **67** in yields of 79-87% (a white foam): $[\alpha]_D$ -28° (c 1.28, $CHCl_3$); IR (film) 3360 (br), 2937, 1695, 1615, 1517, 1454, 1248, 948, 856 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.04-7.09 (m, 2 H), 7.74-6.79 (m, 2 H), 3.99 (m, 1 H), 3.77 (m, 2 H), 3.00 (d, 1 H, $J$ = 13.5 Hz), 2.59 (dd, 1 H, $J$ = 10.5, 13.5 Hz), 1.48-1.64 (m, 6 H), 1.52 (s, 9 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 154.92 (d), 152.10 (d), 130.38 (d), 129.61 (d) 115.44 (d), 93.90 (d), 80.30 (d), 65.80 (d), 59.24 (d), 38.02 (d), 28.48 (d), 27.12 (d), 23.87 (d).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.21; N, 4.56. Found: C, 66.81; H, 8.13; N, 4.49.

**N-Benzyloxycarbonyl-(S)-tyrosinol (69).** To a stirred solution of N-Cbz-L-tyrosine (**68**) (1.26 g, 4.0 mmol) in 40 mL of anhyd THF was added LAH (0.32 g, 8.0 mmol). The reaction mixture was heated at reflux for 3 h, after which the mixture was cooled, quenched with 1 N HCl and diluted with ethyl ether. The ether layer was washed with saturated $NaHCO_3$, then brine, and dried over

$MgSO_4$. The final product was purified on flash chromatography on silica gel with 20% acetone in chloroform to provide 0.50 g (41% yield) of product **69** as a white foam: IR (film) 3600-3200, 2945, 1697, 1615, 1541, 1516, 1456, 1341, 1235, 1059, 824, 739 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.26-7.34 (m, 5 H), 6.99 and 6.70 ($A_2B_2$ doublets, 4 H), 6.05-6.15 (br s, 1 H, NH), 5.06 (s, 2 H, $PhCH_2$), 3.85-3.90 (br, 1 H), 3.65 (dd, 1 H, $J$ = 11.1, 3.8 Hz), 3.52 (dd, 1 H, $J$ = 11.1, 5.5 Hz), 2.76 (d, 2 H, $J$ = 6.9 Hz); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 156.75, 154.66, 136.10, 130.28, 129.02, 128.51, 128.16, 128.01, 115.49, 66.98, 63.90, 54.31, 36.46.

**(4S)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-(p-hydroxyphenylmethyl)oxazolidine (70).** A solution of N-Cbz-(S)-tyrosinol (**69**) (0.50 g, 1.66 mmol), TsOH (0.25 g), DMP (12 mL) in 50 mL of acetone was stirred at rt overnight. The solvent was removed in vacuo and the residue taken up in 100 mL of EtOAc and 20 mL of water. The separated organic layer was washed with saturated $NaHCO_3$ and brine, then dried over anhyd $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography on silica gel with 30% ethyl acetate in hexane to provide 0.37 g (65% yield, an oil) of oxazolidine **70**: $[\alpha]_D$ -54° (c 1.07, $CHCl_3$); IR (film) 3400-3200, 2984, 2942, 1680, 1615, 1595, 1516, 1448, 1417, 1380, 1356, 1257, 1172, 1095, 1020, 962, 863, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 7.33-7.39 (m, 5 H), 6.91 and 6.71 ($A_2B_2$ doubles, 4 H), 5.95 (s, 1 H, OH), 5.14 (s, 2 H, $PhCH_2$), 4.05-4.10 (m, 1 H, α H), 3.79 (d, 2 H, $J$ = 3.0 Hz, $OCH_2$), 3.00 (dd, 1 H, $J$ = 3.0, 12.3 Hz), 2.63 (dd, 1 H, $J$ = 10.5, 13.2 Hz), 1.65 and 1.53, (2 s, 6 H); minor isomer 7.10 and 6.75 ($A_2B_2$ doubles, 2 H), 6.00

(s, 1 H, OH), 5.20 (s, 2 H, $PhCH_2$), 4.10-4.15 (m, 1 H, α H), 3.16 (dd, 1 H, $J$ = 3.0, 12.3 Hz), 1.56 and 1.46 (2 s, 6 H); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ major isomer 154.82, 152.39, 136.18, 130.30, 129.55, 128.52, 128.16, 128.00, 115.44, 94.45, 66.99, 66.24, 59.12, 38.63, 26.60, 23.19; minor isomer 153.01, 135.97, 130.51,128.43, 94.04, 67.38, 65.84, 59.76, 37.40, 27.43, 24.53.

**(4S)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-(4-methoxyphenylmethyl)oxazolidine (71).** A solution of the above oxazolidine **70** (0.37 g, 1.08 mmol), $K_2CO_3$ (0.45 g, 3.3 mmol), MeI (0.47 g, 3.3 mmol) in DMF (8 mL) was stirred at rt overnight, then diluted with EtOAc/water (200 mL/20 mL). The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine and then dried over $MgSO_4$. The product was purified by flash chromatography on silica gel with 20% EtOAc in hexane to provide 0.36 g (93% yield, a white foam) of methyl ether **71**: $[\alpha]_D$ = -51° (c 1.10, MeOH); IR (film) 2983, 2936, 2838, 1703, 1612, 1584, 1514, 1456, 1407, 1379, 1354, 1303, 1248, 1210, 1178, 1148, 1093, 1053, 1036, 863, 832, 765 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 7.38-7.41 (m, 5 H), 7.01 and 6.77 ($A_2B_2$ doubles, 4 H), 5.15 (s, 2 H, $PhCH_2$), 4.05-4.10 (m, 1 H, α H), 3.77-3.80 (m, 2 H, $OCH_2$), 3.03 (dd, 1 H, $J$ = 3.0, 12.3 Hz), 2.63 (dd, 1 H, $J$ = 10.5, 13.2 Hz), 1.66, and 1.52 (2 s, 6 H); minor isomer 7.18 and 6.85 ($A_2B_2$ doubles, 2 H), 5.20 (s, 2 H, $PhCH_2$), 4.09-4.15 (m, 1 H, α H), 3.19 (dd, 1 H, $J$ = 3.0, 12.3 Hz), 1.59 and 1.45 (2 s, 6 H); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ minor isomer 158.16, 152.05, 136.43, 130.10, 128.43, 128.14, 128.00, 127.93, 113.84, 94.22, 66.64, 66.18, 59.01, 55.04 38.66, 26.58, 23.08; minor isomer 152.62, 136.30,

130.32, 129.95, 128.23, 93.75, 66.92, 65.78, 59.71, 54.68, 37.39, 27.42, 24.52.

**(S)-N-Cbz-O-methyltyrosine Methyl Ester (73a).** To a solution of N-Cbz-L-tyrosine (**68**) (0.63 g, 2.0 mmol) in 8 mL of DMF was added 6.0 mmol of $K_2CO_3$ and 10 mmol of MeI. The reaction mixture was stirred at ~60 °C for 3-4 hour, then diluted with water and EtOAc. The aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The product was purified by flash chromatography on silica gel with 25% ethyl acetate in hexane to provide 0.60 g (87% yield, an oil) of ester **73a**: $[\alpha]_D$ 43° (c 0.85, MeOH); IR (film) 3300-3400, 3035, 3008, 2954, 2838, 1724, 1639, 1585, 1515, 1455, 1443, 1380, 1352, 1302, 1245, 1214, 1180, 1111, 1058, 1036, 913, 825 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.32 (br s, 5 H), 7.00 and 6.78 ($A_2B_2$, 4 H), 5.20 (br d, 1 H), 5.08 (s, 2 H), 4.60 (m, 1 H), 3.78 and 3.72 (2 s, 6 H), 3.05 (m, 2 H).

**(S)-N-Boc-O-methyltyrosine Methyl Ester (73b).** A solution of N-Boc-L-tyrosine (**65**) (2.0 mmol) in 10 mL of THF was cooled to 0 °C, and 12 mL of $CH_2N_2$ (~0.4 M in ethyl ether) was added over a period of a few minutes. The reaction mixture was warmed to rt for 3 h, and the solvent was removed in vacuo. Because the $^1H$ NMR spectrum of the crude residue showed only one methyl peak, which was due to methyl ester, the residue was taken up in 8 mL of DMF and treated with 3 mmol of $K_2CO_3$ and 3 mmol of MeI. The mixture was stirred at ~60 °C for 3-4 h and then diluted with water and EtOAc. The aqueous layer was extracted with ethyl acetate. The product was purified by flash chromatography on silica gel with 20% ethyl acetate in hexane to provide 0.55 g (88% yield, an oil) of (S)-N-

Boc-O-methyltyrosine methyl ester (**73b**): $[\alpha]_D$ 5.6° (c 0.60, MeOH); IR (film) 3380-3470, 3107, 2997, 2978, 2956, 2837, 1715, 1614, 1585, 1515, 1442, 1392, 1368, 1302, 1250, 1168, 1111, 1058, 1036, 861 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.05 and 6.84 ($A_2B_2$, 4 H), 4.95 (br d, 1 H), 4.55 (m, 1 H), 3.78 and 3.71 (2 s, 6 H), 3.05 (m, 2 H), 1.42 (s, 9 H).

**N-Cbz-O-methyltyrosinol (74a).** A solution of N-Cbz-O-methyltyrosine methyl ester (**73a**) (0.30 g) in methanol (5 mL) was treated with NaOMe (30 mg) at rt overnight. The solvent was removed in vacuo, and the residue was dissolved in EtOAc and water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was subjected to a short column of silica gel with elution by EtOAc. The ester was dissolved in 5 mL of anhyd ethyl ether, and 2 equiv of LAH was added. The mixture was heated at reflux for 3 h, cooled and quenched with 1 N HCl. The ether layer was washed with saturated $NaHCO_3$ and brine. The final product was purified by flash chromatography on silica gel with 60% ethyl acetate in hexane to provide 0.16 g (59% yield, a white foam) of tyrosinol **74a** with partial racemization: $[\alpha]_D$ -9.1° (c 0.82, EtOAc); IR (film) 3360-3650, 3031, 2934, 1698, 1613, 1585, 1631, 1455, 1344, 1248, 1179, 1037, 813 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, Cbz), 7.10 and 6.83 ($A_2B_2$, 4 H, Tyr), 5.07 (s, 2 H, $PhCH_2$), 5.00 (br d, 1 H, NH), 3.90 (br m, 1 H, α H), 3.78 (s, 3 H, Me), 3.50-3.76 (br m, 2 H, $CH_2O$), 2.79 (d, 2 H, Tyr benzylic), 2.30 (br s, 1 H, OH).

**1-Acetyl-2-(N-benzyloxycarbonylamino)-3-[(4-methoxy)phenyl]propanol (74b).** To a solution of the alcohol **74a** (18 mg) in 1 mL of dichloromethane was added 1 mg of DMAP,

3 equiv of acetic anhydride and 3 equiv of pyridine. The reaction mixture was stirred at rt for 4 h. The solvent was removed in vacuo, and the residue was subjected to a short pad of silica gel to provide 19 mg (100% yield, an oil) of ester **74b**, which was used as a standard racemic sample: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, Cbz), 7.10 and 6.83 ($A_2B_2$, 4 H, Tyr), 5.08 (s, 2 H, $PhCH_2$), 4.90 (br d, 1 H, NH), 4.10 (br m, 1 H, α H), 4.05 (2 s, 2 H, $CH_2O$), 3.78 (s, 3 H, Me), 2.90 (m, 2 H, Tyr benzylic), 2.06 (s, 3 H, $CH_3CO$).

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-D-serine Methyl Ester (76a).** A solution of N-benzyloxycarbonyl-D-serine (**75**) (3.30 g, 13.8 mmol) and p-toluenesulfonic acid (0.45 g) in 80 mL of methanol was heated at reflux for 2-3 h. The solvent was removed in vacuo. The residue was dissolved in 60 mL of acetone and 16 mL of DMP, and another 0.20 g of p-toluenesulfonic acid was added. The reaction mixture was stirred at rt overnight. The acetone was removed in vacuo. The residue was dissolved in 200 mL of EtOAc, then washed with $NaHCO_3$ (saturated) and brine and dried over $MgSO_4$. The ester was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane to give an oil (3.80 g, 94% yield): $[\alpha]_D$ +53° (c 1.20, $CHCl_3$); IR (neat) 3065, 2953, 1757, 1714, 1587, 1499, 1439, 1390, 1247, 1055, 840 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, Cbz rotamers = 3:1) δ major isomer 7.33-7.37 (m, 5 H), 5.15-5.20 (m, 2 H), 4.48 (dd, 1 H, *J* = 6.5, 2.7 Hz), 4.08-4.17 (m, 2 H); 3.64 (s, 3 H); 1.58 and 1.71 (2 s, 6 H); minor isomer 5.04 (d, 2 H), 4.56 (dd, *J* = 6.5, 2.7 Hz), 3.78 (s, 3 H), 1.49 and 1.64 (2 s, 6 H); $^{13}$C NMR (75.44 MHz, $CDCl_3$) δ major isomer 171.02, 151.54, 136.15, 128.23, 127.81, 127.53, 92.23, 66.54, 66.36, 58.65, 52.17, 24.75, 23.91; minor isomer

170.75, 152.61, 135.85, 128.36, 127.98, 94.58, 67.34, 65.95, 59.36, 52.29, 25.86, 24.97.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-L-serine Methyl Ester (76b).** A solution of N-benzyloxycarbonyl-L-serine (**50**) (3.00 g, 11.4 mmol) and p-toluenesulfonic acid (0.45 g) in 80 mL of methanol was heated at reflux for 2-3 h. The solvent was removed in vacuo. The residue was dissolved in 60 mL of acetone and 16 mL of DMP, and another 0.20 g of p-toluenesulfonic acid was added. The reaction mixture was stirred at rt overnight. The acetone was removed in vacuo. The residue was dissolved in 200 mL of EtOAc, then washed with $NaHCO_3$ (saturated) and brine and dried over $MgSO_4$. The ester was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane to give an oil (3.10 g, 91% yield): $[\alpha]_D$ -52° (c 1.10, $CHCl_3$). IR, $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the above sample **76a**.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-D-serinal (78a).** To a stirred solution of N-benzyloxycarbonyl-N,O-isopropylidenyl-D-serine methyl ester (**76a**) (0.98 g, 3.3 mmol) in 12 mL of toluene was added DIBALH (1.0 M in hexane, 7 mL) at -70 °C. The solution was kept at -70 °C for 30-45 min, and then quenched with 0.5 mL of methanol, diluted with 150 mL of EtOAc, washed with 4 x 10 mL of 3 N HCl and 15 mL of brine and dried over $MgSO_4$. The serinal was purified by flash chromatography on silica gel using 5% acetone in chloroform and was obtained as an oil (0.70 g, 79% yield): $[\alpha]_D$ +54° (c 1.05, $CHCl_3$); IR (neat) 3068, 3034, 2985, 2940, 2883, 1713, 1587, 1499, 1456, 1408, 1381, 1353, 1262, 1212, 1162, 1062, 968, 842 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 9.57 (s, 1 H,

CHO), 7.36 (m, 5 H, aromatic), 5.13 (s, 2 H, $PhCH_2$), 4.35 (m, 1 H, α H), 4.14 (m, 2 H, $CH_2O$), 1.68 and 1.58 (2 s, 6 H, 2 x Me); minor isomer 9.66 (s, 1 H, CHO), 5.22 (s, 2 H, $PhCH_2$), 4.45 (m, 1 H, α H), 1.57 and 1.52 (2 s, 6 H, 2 x Me); $^{13}C$ NMR (74.55 MHz, $CDCl_3$) δ major isomer 198.61, 151.72, 135.74, 128.37, 128.03, 127.72, 95.28, 66.92, 64.27, 63.88, 25.48, 23.37; minor isomer 152.12, 128.15, 127.92, 94.57, 67.64, 64.93, 63.31, 26.44, 24.53.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-L-serinal (78b).** To a stirred solution of N-benzyloxycarbonyl-N,O-isopropylidenyl-L-serine methyl ester (**76b**) (1.80 g, 6.14 mmol) in 20 mL of toluene was added dropwise DIBALH (1.0 M in hexane, 9 mL) at -70 °C. The solution was kept at -70 °C for 30-45 min, and then quenched with 1 mL of methanol, diluted with 200 mL of EtOAc, washed with 2 x 15 mL of 6 N HCl, 2 x 15 mL of brine and dried over $MgSO_4$. The serinal was purified by flash chromatography on silica gel using 5% acetone in chloroform and obtained as an oil (1.45 g, 89.8% yield): $[\alpha]_D$ -58° (c 1.37, $CHCl_3$); IR, $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the above sample.

**Synthesis of 2-Methylacrylic Acid Aryl Esters and 2-Methoxyacrylate Aryl Esters (90a-93a). A Typical Procedure**: A solution of substituted phenol **66** (1.10 g, 3.60 mmol), 2-methoxyacrylic acid (0.40 g, 3.90 mmol), DCC (3.0 mmol) and DMAP (3.0 mmol) in 20 mL of benzene (or THF) was heated at reflux for 2-3 h, cooled and stirred overnight. The solution was subjected to a short Celite pad (THF). The solution was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel

using 20% ethyl acetate in hexane to give 1.15 g (82% yield) of ester **93a** as an oil.

**2-Methylacrylic Acid Phenyl Ester (90a).** Product obtained as an oil: IR (neat) 3099, 3066, 3044, 2984, 2960, 2929, 1741, 1638, 1593, 1495, 1456, 1402, 1379, 1322, 1295, 1197, 1164, 1025, 947, 808, 747 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.10-7.39 (m, 4 H), 6.39 (s, 1 H), 5.76 (s, 1 H), 2.07 (s, 1 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 165.54, 150.76, 135.69, 129.17, 126.93, 125.49, 121.40, 18.14.

**2-Methylacrylic Acid p-Methoxyphenyl Ester (91a).** Product obtained as an oil: IR (film) 2960, 1734, 1638, 1597, 1507, 1443, 1296, 1198, 1165, 947, 816, 752 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.88-7.05 (m, 4 H), 6.33 (s, 1 H), 5.73 (s, 1 H), 3.80 (s, 3 H), 2.05 (s, 3 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 166.04, 157.10, 144.30, 135.84, 126.86, 122.23, 114.29, 55.36, 18.26.

**2-Methoxy-2-acrylic Acid Phenyl Ester (92a).** Product obtained as an oil: IR (neat) 2930, 2856, 1745, 1592, 1493, 1385, 1195, 1162, 750 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.13-7.40 (m, 5 H), 5.58 (s, 1 H), 4.81 (s, 1 H), 3.74 (s, 3 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 161.42, 151.46, 150.36, 129.35, 125.92, 121.35, 94.91, 55.74.

**2-Methoxyacrylic Acid 4-{[(4S)-3(t-Butyloxycarbonyl)-2,2-dimethyloxazolidin-4-yl}phenyl Ester (93a).** Product obtained as an oil: $[\alpha]_D$ -31° (c 1.08, $CHCl_3$); IR (film) 2979, 2872, 1757, 1697, 1626, 1509, 1455, 1367, 1201, 1151, 947, 856 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.21-7.30 (m, 2 H), 7.08-7.15 (m, 2 H), 5.56 (s, 1 H), 4.80 (s, 1 H), 3.95-4.15 (m, 1 H), 3.70-3.80 (m, 2 H), 3.73 (s, 3 H), 3.10-3.25 (m, 1 H), 2.62-2.75 (m, 2 H), 1.45-1.62 (m, 6 H), 1.50 (s,

9 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 161.51 (s), 152.08 (s), 151.55 (s), 149.07 (s), 136.29 (s), 130.34 (d), 121.49 (d), 94.97 (d), 93.75 (d), 79.91 (d), 65.91 (d), 59.03 (s), 55.84 (s), 33.49 (d), 28.47 (d), 27.16 (d), 23.82(d).

Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.42; H, 7.48; N, 3.58. Found: C, 64.50; H, 7.57; N, 3.52.

**Synthesis of 2-Methyl-3-aryloxybutadiene and 2-Methoxy-3-aryloxybutadiene (90b-93b).**

**Method A (Petasis' reagent). A Typical Procedure:** A solution of α,β-unsaturated ester **93a** (0.40 g, 1.0 mmol) and $Cp_2TiMe_2$ **96** (3.0 mmol) in THF (8 mL) was heated at reflux for 20 h in the dark. The reaction mixture was cooled to rt, and partitioned with petroleum ether (30-60 °C) and filtered through a short column of silica gel to remove the colored impurities and concentrated. The residue was purified as soon as possible by flash chromatography on basic $Al_2O_3$ (5-30% ether in petroleum ether) to provide 105 mg (26% yield) of diene **93b** as an oil.

**Method B (Tebbe's reagent). A Typical Procedure:** To a solution of α,β-unsaturated aryl ester **93a** (2.50 g, 6.40 mmol) in 18 mL of $PhCH_3$ and 6 mL of THF was added 5 drops of pyridine, afterwhich the solution was cooled to -20 to -30 °C under $N_2$. 18 mL of Tebbe's reagent **98** (~0.5 M in toluene) was added over a few min. The reaction mixture was stirred at -20 to -30 °C for 0.75 h and rt for 2-3 h. The solution was partitioned with 300 mL of petroleum ether (bp 30-60 °C) and filtered through a short column of silica gel (5 in) to remove colored impurities, followed by elution with 20% ethyl acetate in hexane. The combined solutions were concentrated

in vacuo and the residue was again subjected to flash chromatography on silica gel using 10% ethyl acetate in hexane to provide 1.60 g of diene **93b** (64% yield, an oil). Elution with 25% ethyl acetate in hexane resulted in recovery of 0.50 g of the unreacted ester **93a**.

**2-Methyl-3-phenoxybutadiene (90b).** Product obtained as an oil in 31% yield (Method A): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.04-7.37 (m, 5 H), 5.55 (s, 1 H), 5.10 (s, 1 H), 4.78 (s, 1 H), 4.46 (s, 1 H), 2.00 (d, 3 H).

**2-Methoxy-3-phenoxybutadiene (91b).** Product obtained as an oil in 32% yield (Method A) or 41% yield (Method B): $^1$H NMR (300 MHz, $CDCl_3$) δ 6.95-7.24 (m, 5 H), 5.05 (d, 1 H), 4.66 (d, 1 H), 4.38 (d, 1 H) 4.16 (s, 1 H), 3.60 (s, 3 H).

**2-Methyl-3-(p-methoxyphenoxy)butadiene (92b).** Product obtained as an oil in 65% yield (Method B): $^1$H NMR (300 MHz, $CDCl_3$) δ 6.76-7.29 (m, 4 H), 5.63 (d, 1 H), 5.10 (d, 1 H), 4.61 (d, 1 H), 4.23 (d, 1 H), 3.82 (s, 3 H), 2.39 (s, 3 H).

**(4S)-3-(*t*-Butyloxycarbonyl)-2,2-dimethyl-4-[4-(3-methoxy-1,3-butadienyl-2-oxy)phenylmethyl]oxazolidine (93b).** Product obtained as an oil: $[\alpha]_D$ -26° (c 0.70, $CHCl_3$); IR (film) 2938, 1698, 1592, 1508, 1454, 1366, 1200, 1149, 1053, 963, 856 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.10-20 (m, 2 H), 6.95-7.00 (m, 2 H), 5.11 (d, 1 H), 4.74 (s, 1 H), 4.43 (d, 1 H), 4.24 (s, 1 H), 3.95-4.10 (m, 1 H), 3.70-3.79 (m, 2 H), 3.67 (s, 3 H), 3.05-3.20 (m, 1 H), 2.60-2.70 (m, 1 H), 1.46-1.63 (m, 6 H), 1.52 (s, 9 H); $^{13}$C NMR (74.55 MHz, $CDCl_3$) 155.55 (s), 155.10 (d), 154.70 (d), 151.83 (d), 133.26 (s),

130.40 (d), 118.82 (s), 94.33 (d), 93.73 (d), 83.81 (s), 79.81 (d) 65.88 (d), 59.10 (s), 55.07 (s), 38.29 (d), 28.45 (d), 27.10 (d), 23.32 (d).

**Petasis' Reagent (96).** A solution of $Cp_2TiCl_2$ (0.50 g, 2.0 mmol) in 10 mL of ethyl ether was cooled to -20 °C under $N_2$, and 3.6 mL of MeLi (1.4 M in ethyl ether) was added in a few minutes. The reaction mixture was stirred at rt for 45 minutes, quenched with water and then diluted with ethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the crude product (0.42 g, 92% yield) was used in the next step after being dried in high vacuum for a half hour. (The product is light sensitive).

**Tebbe's Reagent (98).** To 2.50 g (10 mmol) of $Cp_2TiCl_2$ in adried flask was added 10 mL (20 mmol) of $AlMe_3$ (2.0 M in toluene) under $N_2$. The solution was allowed to stand 48-60 h at room temperature. The residue was diluted with 20 mL of freshly distilled toluene to provide a ~0.5 M solution of Tebbe's reagent.

**(S)-*t*-Butyl 2,2-dimethyl-[4-(2-ketopropyl)oxyphenyl methyl]-3-oxazolidinecarboxylate (100).** To a solution of phenol **66** (1.04 g, 3.38 mmol) and $K_2CO_3$ (0.52 g, 3.72 mmol) in 10 mL of dried acetone was added a solution of $ClCH_2COCH_3$ (0.38 g, 4.11 mmol) and KI (33 mg, 0.05 mol %) in 3 mL of acetone. The reaction mixture was heated at reflux for 7 h and stirred overnight at rt. The mixture was passed through a short pad of silica gel (EtOAc) and concentrated. The residue was subjected to MPLC on silica gel using 30% ethyl acetate in hexane to give 0.95 g (77% yield, a white foam) of product: $[\alpha]_D$ -31° (c 0.80, $CHCl_3$); IR (film) 2980, 2933, 2871, 1723, 1697, 1613, 1586, 1511, 1479, 1455, 1387, 1366, 1307, 1257,

1209, 1173, 1149, 1094, 1077, 1053, 1019, 949, 857, 807, 769 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.11-7.19 (m, 2 H), 6.80-6.84 (m, 2 H), 4.52 (s, 2 H, $PhCH_2$) 3.95 and 4.05 (two br s, 1 H), 3.75 (m, 2 H), 3.12 and 3.16 (two br s, 1 H, *J* = 13.2 Hz), 3.01 and 3.05 (two br s, 1 H, *J* = 13.2 Hz), 2.58-2.66 (dd, *J* = 10.5, 13.2 Hz), 1.52 (s, 9 H, Boc), 1.46-1.62 (series of s, 6 H, 2 x Me); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ major isomer 204.93, 156.09, 151.16, 131.22, 130.21, 114.28, 93.51, 78.08, 72.57, 65.34, 58.74, 38.32, 28.09, 26.42, 26.00, 22.78; minor isomer 204.81, 151.62, 130.00, 114.12, 93.06, 79.51, 65.55, 37.20, 27.08, 24.11.

**2-Phenoxy-1,3-butanedione (103).** Sodium (0.28 g, 12 mmol) was added in portions to 8 mL of absolute EtOH. To this solution at 0 °C was added a solution of 1-phenoxyacetone (**101**) (1.50 g, 10.0 mmol) and ethyl formate (0.89 g, 12 mmol). The reaction mixture was stirred at rt overnight. The mixture was poured into 25 mL of 0.5 N HCl. The product was extracted by ethyl ether (2 x 50 mL) from the aqueous phase. The separated organic phase was washed with 1 N HCl and brine, then dried over $MgSO_4$. Ketone **103** was obtained by MPLC on silica gel using 30% ethyl acetate in hexane to give 1.10 g (62% yield) of product, with 10% of unreacted starting material also being isolated. The product (an oil) can also be purified by distillation (88-92 °C/0.25 mmHg) and used directly in the next step: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1 H, CHO), 6.93-7.32 (m, 6 H), 2.09 (s, 3 H).

**1,3-Bis[(trimethylsilyl)oxy]-2-phenoxy-1,3-butadiene (105).** A solution of diketone **103** (0.42 g, 2.35 mmol) and triethylamine (1.8 mL, 12.8 mmol) in absolute ethyl ether (15 mL)

was cooled to -20 °C under $N_2$, after which 1.0 mL (5.2 mmol) of TMSOTf was added over a few min via syringe. The reaction mixture was stirred for 30 min at -20 °C, then rt for 2 h and diluted with hexane. The hexane layer was subjected to a short pad of $Na_2SO_4$. The final diene (0.60 g, 79% yield, an oil) was obtained by evaporating the solvent and was immediately used for the next step: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.22-7.25 (m, 2 H), 6.95-6.98 (m, 3 H), 6.72 (s, 1 H), 4.46 (d, $J$ = 0.9 Hz), 4.18 (d, $J$ = 0.9 Hz), 0.26 (s, 9 H), 0.11 (s, 9 H).

**Diels-Alder Cycloadditions of Aryloxy Dienes with Methyl Acrylate or Dimethyl Acetylenedicarbonylate (111a, 112a, 114a & 115a). A Typical Procedure**: A solution of 2,3-disubstituted diene **90b** (50 mg, 0.31 mmol) and methyl acrylate (**107**) (0.20 g, 1.2 mmol) in 0.5 mL of toluene was heated at reflux for 20 h. TLC indicated the reaction was complete. The reaction mixture was subjected to flash chromatography on silica gel to provide 60 mg (71% yield) of substituted cyclohexadiene **111a** as an oil. The structure of the diene was confirmed by only $^1$H NMR and oxidized by DDQ in the next step.

**5-Methyl-4-phenoxy-1,4-cyclohexadienecarboxylic Acid Methyl Ester and 4-Methyl-5-phenoxy-(1,4)-cyclohexadienecarboxylic Acid Methyl Ester (111a).** Product obtained as an oil in 71% yield: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.91-7.28 (m, 5 H), 3.75 (2 s, 3 H), 2.95-3.15 (m, 4 H) 1.66 (2 s, 3 H).

**5-Methoxy-4-phenoxy-1,4-cyclohexadienecarboxylic Acid Methyl Ester and 4-Methoxy-5-phenoxy-(1,4)-cyclohexadienecarboxylic Acid Methyl Ester (112a).**

Product obtained as an oil in 85% yield: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.90-7.45 (m, 6 H), 3.68-3.79 (3 s, 6 H), 3.05-3.40 (m, 4 H).

**5-Methyl-4-phenoxy-1,4-cyclohexadiene-1,2-dicarboxylic Acid Dimethyl Ester (114a).** Product obtained as an oil in 93% yield: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.88-7.31 (m, 5 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.05-3.17 (m, 4 H), 1.67 (s, 3 H).

**5-Methyl-4-[4-methoxy-phenoxy]-(1,4)-cyclohexadiene-1,2-dicarboxylic Acid Dimethyl Ester (115a).** Product obtained as an oil in 95% yield: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 4 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.73 (s, 3 H) 3.00-3.19 (m, 4 H), 1.69 (s, 3 H).

**Oxidation of Cycloadducts with DDQ. A Typical Procedure:** Cyclohexadiene **111a** (60 mg, 0.25 mmol) was oxidized by DDQ (0.11 g, 0.50 mmol) at reflux in benzene (3 mL) solution for 2 h. The reaction mixture was subjected to flash chromatography on silica gel to provide a quantitative yield of substituted diaryl ether **111b** as an oil. The product was confirmed by IR, $^1$H NMR, $^{13}$C NMR and combustion analyses.

**4-Methyl-3-phenoxybenzoic Acid Methyl Ether and 3-Methyl-4-phenoxybenzoic Methyl Ester (111b).** Product obtained as an oil in 100% yield: IR (film) 3064, 3039, 2993, 2952, 2923, 2849, 1723, 1587, 1489, 1436, 1408, 1383, 1293, 1204, 1177, 1124, 1094, 1023, 905, 853, 837, 794, 761 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.69-7.95 (m, 8 H), 3.87 (d, 3 H), 2.32 (d, 3 H).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.35; H, 5.85. Found: C, 74.49; H, 5.90.

**4-Methoxy-3-phenoxybenzoic Acid Methyl Ester and 3-Methoxy-4-phenoxybenzoic Acid Methyl Ester (112b).** Product obtained as an oil in 93% yield: IR (neat) 2950, 2841, 1718, 1587, 1508, 1489, 1456, 1292, 1217, 1177, 1029, 989, 762 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.90-7.90 (m, 8 H), 3.85-3.95 (4 s, 6 H).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.47. Found: C, 70.02; H, 5.54.

**5-Methyl-4-phenoxyphthalic Acid Dimethyl Ester (114b).** Product obtained as an oil in 93% yield: IR (neat) 3063, 2951, 1730, 1575, 1489, 1435, 1233, 1125, 935, 787 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.97-7.68 (7 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 2.35 (s, 3 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 167.63, 167.21, 157.48, 155.75, 132.42, 131.86, 131.79, 129.89, 125.48, 123.91, 118.81, 117.14, 52.42, 52.32, 16.02.

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.98; H, 5.38. Found: C, 67.80; H, 5.41.

**5-Methyl-4-[4-methoxyphenoxy]phthalic Acid Dimethyl Ester (115b).** Product obtained as an oil in 97% yield: IR (neat) 3106, 2839, 1733, 1613, 1595, 1505, 1435, 1234, 1153, 934, 851 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 7.67 (s 1 H) 6.89-6.94 (m, 5 H), 3.88 (s, 3 H) 3.82 (s, 6 H), 2.37 (s, 3 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 167.77, 166.91, 158.76, 156.21, 148.43, 132.07, 131.96, 130.46, 124.15, 120.74, 114.92, 114.83, 55.20, 52.24, 52.08, 15.85.

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.50. Found: C, 65.61; H, 5.42.

**3-Hydroxy-4-phenoxybenzoic Acid Methyl Ester**

**(116).** A solution of 1,2,3-trisubstituted diene **105** (96 mg, 0.30 mmol) and methyl propiolate (50 mg, 0.60 mmol), in 0.25 mL of toluene containing a trace of hydroquinone, was heated at reflux for 15 h. The toluence was removed in vacuo. The reaction mixture was treated with a mixture of 4 mL of THF and 1 mL of 0.5 N HCl, then diluted with 150 mL of ethyl ether. The ether layer was washed with brine and dried over $Na_2SO_4$. The residue was subjected to flash chromatography on silica gel to provide 29 mg (40% yield, an oil) of substituted diaryl ether: $^1$H NMR (270 MHz, $CDCl_3$) δ 7.05-7.85 (m, 8 H), 6.05 (br s, 1 H) 3.85 (s, 3 H). The obtained phenol **116** was transferred into methyl ether for characterization.

**3-Methoxy-4-phenoxybenzoic Acid Methyl Ester (117).** To a solution of diaryl ether **116** (11 mg) in 0.5 mL of DMF was added $K_2CO_3$ (3 equiv) and MeI (3 equiv). The solution was stirred at rt overnight; the work-up provided enough sample (an oil) for $^1$H NMR spectrum (300 MHz, $CDCl_3$): δ 6.90-7.90 (m, 8 H), 3.91 (s, 3 H), 3.85 (s, 3 H). $^1$H NMR and TLC were superimposable to the one regioisomer (low $R_f$) of compound **112b**, which has been fully characterized.

**Benzyl (R)-4-(1-Oxo-2-propynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (119).** To a stirred solution of N-benzyloxycarbonyl-N,O-isopropylidenyl-L-serinal (**78b**) (0.72 g, 2.74 mmol) in dry THF (30 mL) ethynyl magnesium chloride (8.0 mL, 0.5 M in THF) was slowly added. The reaction mixture was stirred at rt for 2 h, quenched with water and diluted with ethyl ether. The organic phase was washed with 1 N HCl and brine, dried over $MgSO_4$ and evaporated to an oil. This product may be used crude for next

step or purified by flash chromatography on silica gel with 25/75 EtOAc/Hexane to provide a mixture of diastereomers of alcohol **123** (0.68) in 86% yield: $[\alpha]_D$ -41.0° (c 0.88, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of two diastereomers) δ 7.41 (br s, 5 H), 5.22 (m, 2 H, $PhCH_2$), 4.65 (br s, 1 H), 3.80-4.40 (m, 3 H), 2.47 (2 s, 1 H), 1.47-1.70 (m, 6 H, 2 x Me).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.63; N 4.84. Found: C, 66.34; H, 6.54; N, 4.83.

To a stirred solution of alcohol **123** (0.80 g, 2.77 mmol) in 20 mL of ethyl ether was added 5.0 mL of Jones' reagent in 2 min at 0 °C. The reaction mixture was stirred for another 15-20 min at rt and diluted with 150 mL of ethyl ether. The organic layer was washed with $NaHCO_3$ (saturated) and brine, dried over $MgSO_4$ and evaporated to an oil. The product was purified by flash chromatography on silica gel with 30% ethyl acetate in hexane to provide alkyne **119** (0.63 g) as an oil in 79% yield: $[\alpha]_D$ -58° (c 1.26, $CHCl_3$); IR (neat) 3350, 3068, 3035, 2989, 2890, 1797, 1713, 1588, 1499, 1456, 1408, 1382, 1352, 1268, 1255, 1211, 1165, 1110, 1092, 1040, 951, 911, 843, 766 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 7.25-7.37 (m, 5 H, ArH), 5.11 (s, 2 H, $PhCH_2$), 4.52 (t, 1 H, $J$ = 5.1 Hz, α H), 4.20 (s, 2 H, $OCH_2$), 3.30 (s, 1 H), 1.57 and 1.73 (2 s, 6 H); minor isomer 5.20 ($A_2B_2$ q, 2 H, $PhCH_2$), 4.64 (dd, 1 H, $J$ = 6.3, 3.3 Hz), 4.18 (s, 2 H, $OCH_2$), ~~4.18 (s, 2 H, $OCH_2$)~~, 1.65 and 1.50 (2 s, 6 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ major isomer 184.59, 151.60, 135.78, 128.30, 127.97, 127.84, 95.71, 82.74, 79.15, 66.89, 66.01, 65.49, 25.03, 23.70; minor isomer 183.91, 152.77, 128.50, 128.41, 128.10, 95.02, 82.26, 67.54, 66.82, 64.92, 26.02, 25.61.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.98; N, 4.88. Found: C, 66.75; H, 5.98; N, 4.80.

**Benzyl (R)-4-(1-Oxo-2-propynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (120).** To a stirred solution of N-benzyloxycarbonyl-N,O-isopropylidenyl-D-serinal (**78a**) (1.80 g, 6.84 mmol) in dry THF ethynylmagnesium chloride (20 mL, 0.5 M in THF) was slowly added. The reaction mixture was stirred at rt for 1 hour and heated at reflux for 1 h, quenched with water and diluted with 300 mL ethyl ether. The organic phase was washed with 1 N HCl and brine, dried over $MgSO_4$ and evaporated to an oil. This product may be used crude for the next step or purified by flash chromatography on silica gel with 25% ethyl acetate in hexane to provide a mixture of diastereomers of alcohol **122** (1.75 g, an oil) in 88.5% yield: $[\alpha]_D$ 38.9° (c 1.22, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of two diastereomers) δ 7.37 (br s, 5 H, PhH), 5.20 (m, 2 H, $PhCH_2$), 4.65 (br m, 1 H), 3.90-4.35 (m, 3 H), 2.47 (2 s, 1 H, due to different diastereomers), 1.50-1.70 (series of s, 6 H, 2 x Me).

To a stirred solution of alcohol **122** (0.40 g, 1.40 mmol) in 5 mL of ethyl ether was added 4 mL of Jones' reagent over a few min. The reaction mixture was stirred for another 15 min, diluted with 150 mL of ethyl ether, washed with water and brine, dried over $MgSO_4$ and evaporated to an oil. The product was purified by flash chromatography on silica gel with 25% ethyl acetate in hexane to provide alkyne **120** (0.33 g, an oil) in 83% yield: $[\alpha]_D$ 53° (c 1.26, $CHCl_3$); $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the sample

**N-Benzyloxycarbony-N,O-isopropylidenyl-β-oxo-(R)-tyrosinol (125a).** A solution of the alkyne **120** (0.21 g, 0.73 mmol) and Danishefsky's diene (0.20 g, 1.2 mmol) in 3 mL of toluene was heated at reflux overnight. The toluene was removed in vacuo. The residue was treated with a mixture of 4 mL of THF and 1 mL of 0.2 N HCl for 45 min. The reaction mixture was diluted with ethyl ether, washed with brine, dried over $MgSO_4$ and evaporated to a yellow foam. The product was purified by flash chromatography on silica gel with 40% ethyl acetate in hexane to provide **125a** (0.22 g, a white foam) in 85% yield: $[\alpha]_D$ 43° (c 1.21, MeOH), $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the sample **125b**.

**N-Benzyloxycarbony-N,O-isopropylidenyl-β-oxo-(S)-tyrosinol (125b).** A solution of the alkyne **119** (0.26 g, 0.90 mmol) and Danishefsky's diene (0.25 g, 1.2 mmol) in 8 mL of toluene was heated at reflux overnight. The toluene was removed in vacuo, after which the residue was treated with a mixture of 4 mL of THF and 1 mL of 0.2 N HCl for 45 min. The reaction mixture was diluted with ethyl ether, washed with brine, dried over $MgSO_4$ and evaporated to a yellow solid. The product was purified by flash chromatography on silica gel with 40% ethyl acetate in hexane to provide tyrosinol **125b** (0.29 g) as a white foam in 90% yield: $[\alpha]_D$ -39° (c 0.80, MeOH); IR ($CHCl_3$) 3020 2895, 1707, 1605, 1587, 1516, 1475, 1382, 1215, 1171, 1068, 1050, 830, 849 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.12-7.40 (m, 5 H), 6.68 and 7.62 (2 d, 4 H), 5.43 (dd, 1 H), 5.22 (q, 2 H) 4.34 (t, 1 H, $J$ = 8.7 Hz) 3.93-4.02 (dt, 1 H, $J$ = 3.0, 9.3 Hz), 1.57 and 1.74 (2 s, 6 H); minor isomer 6.84 and 7.73 (2 d, 4 H), 5.37 (q, 1 H) 5.01 (q, 2 H), 1.63 and 1.80 (2 s, 6 H); $^{13}C$ NMR (75.44

MHz, $CDCl_3$) δ major isomer 192.63, 160.84, 153.40, 135.69, 130.86, 128.65, 128.28, 128.07, 127.57, 115.72, 95.25, 68.08, 66.18, 61.79, 25.61, 24.47; minor isomer 193.62, 161.40, 151.98, 136.13, 128.33, 127.79, 127.44, 126.65, 95.67, 66.82, 66.59, 61.14, 25.44, 24.71.

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.58; H, 5.97; N, 3.94. Found: C, 67.68; H, 6.09; N, 3.89.

**N-Benzyloxycarbony-N,O-isopropylidenyl-β-oxo-O-methyl-(R)-tyrosinol (126a).** A solution of phenol **125a** (0.24 g, 0.68 mmol), $K_2CO_3$ (0.28 g, 2.0 mmol, 3 equiv) and MeI (0.28 g, 2.0 mmol, 3 equiv) in DMF (10 mL) was stirred at rt overnight, then diluted with EtOAc/water. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine, then dried over $MgSO_4$. The product was purified by flash chromatography on silica gel with 40% ethyl acetate in hexane to provide 0.22 g (88% yield) of methyl ether **126a** as a white foam: $[\alpha]_D$ 43° (c 1.21, MeOH); IR ($CHCl_3$) 2939, 2884, 1709, 1601, 1512, 1456, 1348, 1175, 1050, 933, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 6.90-7.94 (m, 9 H), 5.39 (dd, 1 H, $J$ = 3.3, 7.5 Hz), 5.01 (q, 2 H, $J$ = 12.5 Hz), 4.34 (dd, 1 H, $J$ = 7.5, 9.1 Hz), 3.99 (dd, 1 H, $J$ = 3.3, 9.1 Hz), 3.88 (s, 3 H) 1.63 and 1.80 (2 s, 6 H); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ 193.59, 163.79, 151.78, 136.19, 130.51, 128.19, 127.93, 127.66, 127.51, 113.98, 95.53, 66.62, 65.28, 61.03, 55.47, 24.65, 24.41; minor isomer 193,17, 152.73, 128.50, 125.05, 94.85, 67.42, 60.09, 61.85, 25.76, 25.47.

**N-Benzyloxycarbony-N,O-isopropylidenyl-β-oxo-O-methyl-(S)-tyrosinol (126b).** A solution of phenol **125b** (0.23 g, 0.65 mmol), $K_2CO_3$ (0.27 g, 1.95 mmol, 3 equiv), MeI (0.28 g, 2.0

mmol, 3 equiv) in DMF (10 mL) was stirred at rt overnight, then diluted with EtOAc/water. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine, then dried over $MgSO_4$. The product was purified by flash chromatography on silica gel with 33% ethyl acetate in hexane to provide 0.20 g (82% yield, a white foam) of methyl ether **126b**: $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the above sample **126a**.

**(R)-Benzyl 4-(4-Methoxyphenylmethyl)-2,2-dimethyl-3-oxazolidinecarboxylate (128a).** To a solution of ketone **126a** (0.20 g, 0.54 mmol) in 8 mL of THF/MeOH (1:1) was added $NaBH_4$ (0.2 g, excess) at rt. The reaction mixture was stirred for 1-2 h, and the reaction was checked by TLC. The solvent was removed in vacuo, and the residue was dissolved in EtOAc/water (100 mL/10 mL). The organic layer was washed by brine and dried over $MgSO_4$. The alcohol product was purified by flash chromatography on silica gel with 40/60 EtOAc/hexane to provide a mixture of diastereomers (0.18 g, an oil) in 90% yield: $[\alpha]_D$ -3.7° (c 1.20, $CHCl_3$); IR (film) 3300-3500, 2939, 2837, 1697, 1613, 1586, 1514, 1456, 1411, 1381, 1353, 1304, 1250, 1211, 1175, 1096, 1071, 1047, 913, 842, 767 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of diastereomers) δ 7.42 (m, 7 H), 6.91 (d, 2 H), 5.26 (s, 2 H, $PhCH_2$), 4.78 (br d, 1 H), 4.30 (br m, 1 H), 3.82 (s, 3 H, $OCH_3$), 3.70-3.82 (br m, 2 H), 1.57 and 1.51 (2 s, 6 H, 2 x Me).

To a solution of the above alcohol (140 mg, 0.38 mmol) in 3 mL of dichloroethylene was added $(Im)_2S{=}C$ (113 mg, 0.57 mmol) and DMAP (15 mg). The solution was heated at reflux for 7 h under

nitrogen, and the reaction was checked by TLC. The solution was concentrated and the residue was subjected to flash chromatography on silica gel with 40/60 EtOAc/hexane to provide ester (129 mg) as a yellow foam in 71% yield: IR (film) 3070, 3033, 2978, 2938, 2884, 1698, 1611, 1584, 1514, 1470, 1403, 1381, 1350, 1293, 1256, 1224, 1180, 1151, 1097, 1072, 1031, 961, 887, 837, 755 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of diastereomers) δ 8.00-8.19 (3 s, 1 H), 6.80-7.60 (m, 11 H), 5.10-5.55 (m, 3 H), 4.35-4.40 (m, 1 H), 3.90-4.15 (m, 2 H), 3.80 (s, 3 H, $OCH_3$), 1.35 -1.77 (sets of s, 6 H, 2 x Me).

A solution of the above ester (114 mg, 0.24 mmol) and AIBN (8 mg) in benzene was degassed with $N_2$ for 10 min; then 800 μL (excess) of tributyltin hydride was added. The solution was heated at reflux for 2-3 h. The reaction mixture was cooled down, concentrated and subjected to flash chromatography on silica gel with 0-20% EtOAc/ hexane to provide (S)-tyrosinol oxazolidine **128a** (71 mg) as an oil in 83% yield: $[\alpha]_D$ -50° (c 0.70, $CHCl_3$); $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the standard sample **71**.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.10; N, 3.94. Found: C, 70.70; H, 7.08; N, 3.96.

**N-Benzyloxycarbonyl-O-methyl-(S)-tyrosinol (129a).** A solution of oxazolidine **130a** (50 mg) or **128a** and TsOH (10 mg) in 5 mL of MeOH was stirred at rt overnight. The solvent was removed in vacuo, and the residue was subjected to flash chromatography on silica gel with 50/50 EtOAc/hexane to provide tyrosinol **129a** (40 mg) in 93% yield: $[\alpha]_D$ -39° (c 0.98, MeOH); $^1H$ NMR, and TLC were

superimposable to the above sample **74a**; $^{13}C$ NMR (67.90 MHz, $CDCl_3$): δ 158.15, 156.47, 136.27, 130.13, 129.56, 128.38, 127.99, 127.88, 113.85, 66.64, 63.54, 55.09, 54.15, 36.28.

**(S)-Benzyl 4-(4-Methoxyphenylmethyl)-2,2-dimethyl-3-oxazolidinecarboxylate (130a).** A solution of ketone **126a** (151 mg, 0.41 mmol), $NaCNBH_3$ (194 mg, 3.07 mmol, 7.5 equiv) and $ZnI_2$ (199 mg, 0.62 mmol, 1.5 equiv) in 5 mL of dichloroethylene was heated at reflux for 7-11 h. The reaction was checked by TLC. After the reaction mixture was cooled down, the solution was subjected to a short Celite pad, and the product was purified by flash chromatography on silica gel with 25/75 EtOAc/Hexane to provide product (60 mg) as an oil in 41% yield: $[\alpha]_D$ -38° (c 1.30, $CHCl_3$).

**(R)-Benzyl 4-(4-Methoxyphenylmethyl)-2,2-dimethyl-3-oxazolidinecarboxylate (130b).** A solution of ketone **126b** (58 mg, 0.16 mmol), $NaCNBH_3$ (75 mg, 1.2 mol, 7.5 equiv) and $ZnI_2$ (77 mg, 0.24 mmol, 1.5 equiv) in 2 mL of dichloroethylene was heated at reflux for 20 h. The reaction was checked by TLC. After the reaction mixture was cooled down, the solution was subjected to a short Celite pad, and the product was purified by flash chromatography on silica gel with 25/75 EtOAc/hexane to provide product (30 mg) as an oil in 53% yield: $[\alpha]_D$, 32° (c 1.00, MeOH) $^1H$ NMR, $^{13}C$ NMR and TLC were superimposable to the above sample.

**N-Benzyloxycarbonyl-O-methyl-(S)-tyrosine (131a).** To a solution of tyrosinol **130a** (31 mg) in ethyl ether (2 mL) was added 1 mL of Jones' reagent at rt. The reaction mixture was stirred for 2 h and diluted with ethyl ether. The organic layer was washed with 3 x 10 mL brine and dried over $MgSO_4$. The acid was obtained by flash

chromatography on silica gel with 20-100% ethyl acetate in hexane to provide 20 mg of **131a** in 61% yield (a white foam): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.33-7.37 (m, 5 H, $PhCH_2$), 6.80 and 7.05 ($A_2B_2$, 4 H, Tyr), 5.15 (br s, 1 H, NH), 5.11 (s, 2 H, $CH_2$), 4.60-4.65 (m, 1 H, α H) 3.77 (s, 3 H, OMe), 3.05-3.10 (m, 2 H, Tyr benzylic).

**Mosher's amides 133 and 134 of O-methyltyrosinols.** N-Cbz-O-methyltyrosinol (**74a**, **74b**, **128a**, **129a**, **130a**, and **130b**) (0.050-0.10 mmol) was treated with 1 mL of HBr in HOAc for 1 h. The acetic acid was removed in vacuo. The residue was dried in high vacuo for 1-2 h and dissolved in 1 mL of $CH_2Cl_2$. The solution was cooled in 0 °C, followed by addition of Mosher's acid (1.0 equiv), HOBt (1.0 equiv), $Et_3N$ (1.0 equiv) and EDCI (1.0-2.0 equiv). The reaction mixture was stirred at 0 °C for 2-3 h and rt overnight. The solvent was removed in vacuo, and the residue was dissolved in EtOAc/$H_2O$. The organic phase was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine, then dried over $MgSO_4$. $^1$H NMR spectra of the crude products showed that the chemical shift of methoxy group of Mosher's amide for (R)-tyrosinol was 3.32 ppm, whereas (S)-tyrosinol was 3.28 ppm.

**N-Benzyloxycarbonyl-β-hydroxy-N,O-isopropylidenyl-O-methyl-(R)-tyrosinol (135b).** A solution of ketone **126a** (0.44 g, 1.24 mmol) in 10 mL of THF and 10 mL of methanol was cooled to 0 °C, followed by addition of $NaBH_4$ (0.40 g, excess) in three portions in one half hour. The reaction mixture was kept at 0 °C for 1 h and rt for another hour. The solvent was removed in vacuo, after which the residue was dissolved in 150 mL of EtOAc and 20 mL of water. The organic phase was washed with 1 N HCl and brine, then dried over $MgSO_4$. The solution was removed in vacuo, and the residue was

subjected to a short pad of silica gel (30% ethyl acetate in hexane) to provide 0.40 g (90% yield) of benzyl alcohol **135b** as an oil: IR (film) 3300-3500, 2939, 2837, 1697, 1613, 1586, 1514, 1456, 1411, 1381, 1353, 1304, 1250, 1211, 1175, 1096, 1071, 1047, 913, 842, 767 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of diastereomers) δ 7.42 (m, 7 H), 6.91 (d, 2 H), 5.26 (s, 2 H, $PhCH_2$), 4.78 (br d, 1 H), 4.30 (br m, 1 H), 3.82 (s, 3 H, $OCH_3$), 3.70-3.82 (br m, 2 H), 1.57 and 1.51 (2 s, 6 H, 2 x Me).

**(1R,2R)-2-(N-Benzyloxycarbonylamino)-1-[(4-methoxy)phenyl]-1,3-propanediol (136b).** To a solution of benzyl alcohol **135b** (0.40 g) in 10 mL of methanol was added TsOH (35 mg). The reaction mixture was stirred at rt overnight. The methanol was removed in vacuo. Thus the residue was subjected to MPLC on silica gel using 60% ethyl acetate in hexane to provide diol **135b** (0.33 g, a white foam) as a major diastereomer in 86% yield: $[\alpha]_D$

-41° (c 0.85, MeOH); IR (film) 3200-3500, 2954, 1699, 1613, 1514, 1456, 1248, 1177, 1031, 834, 740 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to the ratio of diastereomers) δ 7.33 and 6.85 ($A_2B_2$, 4 H, Tyr), 7.26 (m, 5 H, Cbz), 5.68 (br d, 0.3 H, NH), 5.55 (br s, 0.7 H, NH), 5.08 (s, 0.3 H, $PhCH_2$), 5.01 (s, 0.7 H, $PhCH_2$), 4.92 (d, 1 H, $J$ = 3.6 Hz), 3.79 (s, 3 H, Me), 3.70-3.90 (m, 3 H), 2.80 (br s, 2 H).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.23; H, 6.40; N, 4.23. Found: C, 65.34; H, 6.49; N, 4.30.

**Diels-Alder Adduct 139a and 139b.** A solution of 2-methoxy-3-phenoxy-1,3-butadiene (**92b**) (0.12 g, 0.68 mmol) and alkyne **120a** (0.19 g, 0.66 mmol) in 1 mL of toluene containing a

trace of hydroquinone was heated at 150 °C (oil temperature) in a sealed tube for 60 h. The reaction mixture was subjected to flash chromatography on silica gel with 30% ethyl acetate in hexane to provide two regioisomers (ratio = 1:1): 0.10 g of **139a** ($R_f$ 0.12, an oil) and 0.11 g of **139b** ($R_f$ 0.28, an oil) in 70% overall yield.

**Oxidation of 139a and 139b by DDQ. A Typical procedure:** The cyclohexadiene (0.11 g, 0.24 mmol, $R_f$ 0.28) was oxidized by DDQ (0.15 g, 0.70 mmol) in a benzene (5 mL) solution heated at reflux for 2 h. Purification by flash chromatography on silica gel with gradient elution (5-30% ethyl acetate in hexane) provided 85 mg of diaryl ether in 78% yield (a white foam). One of the regioisomers (**140b**) was completely characterized by IR, $^1$H NMR, $^{13}$C NMR and combustion analyses.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-β-oxo-O-methyl-3-phenoxy-(R)-tyrosinol (140a).** This compound was obtained as a white foam: $[\alpha]_D$ 14° (c 1.25, $CHCl_3$); IR (film) 2983, 1713, 1601, 1576, 1514, 1490, 1456, 1379, 1266, 1138, 1052, 752 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) major isomer 6.93-7.79 (m, 13 H), 5.31 (dd, 1 H, $J$ = 7.5, 3.3 Hz), 5.01 (q, 2 H, $J$ = 12.5 Hz), 4.28 (dd, 1 H, $J$ = 7.5, 9.0), 3.95 (dt, 1 H, $J$ = 9.0, 3.0), 3.92 (s, 3 H), 1.61 and 1.76 (2 s, 6 H); minor isomer 5.39 (dd, 1 H, $J$ = 7.5, 3.3), 5.15 (q 1 H, $J$ = 12.5 Hz), 1.51 and 1.69 (2 s, 6 H). $^{13}$C NMR was identical with phenol **141**, except that the spectrum of **140a** showed a peak due to the O-methyl group.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-β-oxo-3-methoxy-4-phenyl-(R)-tyrosinol (140b).** This compound was obtained as a white foam: IR (film) 2987, 2940, 1712, 1585, 1507,

1489, 1464, 1411, 1379, 1347, 1268, 1200, 1170, 1140, 1094, 1068, 1152, 821, 750 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ major isomer 6.78-7.70 (m, 12 H), 5.38 (dd, 1 H, *J* = 7.5, 3.3 Hz), 5.04 (q, 2 H, *J* = 12.5 Hz), 4.32 (m, 1 H), 3.95 (dt, 1 H, *J* = 9.0, 3.0), 3.91 (s, 3 H), 1.63 and 1.81 (2 s, 6 H); minor isomer 5.49 (dd, 1 H, *J* = 7.5, 3.3), 5.20 (q, 1 H, *J* = 12.5 Hz), 3.93 (s, 3 H), 1.56 and 1.74 (2 s, 6 H); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ major isomer 194.04, 155.96, 152.90, 151.31, 150.90, 136.26, 130.37, 129.92, 128.59, 128.28, 127.77, 124.24, 121.89, 119.18, 117.71, 112.05, 95.70, 66.77, 66.56, 61.16, 56.13, 25.56, 24.72; minor isomer 193.61, 156.05, 151.80, 136.26, 130.45, 128.17, 128.01, 127.83, 124.15, 122.14, 117.82, 112.24, 95.00, 67.56, 66.12, 61.95, 55.45, 25.80, 24.49.

Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.26; H, 5.91; N, 3.04. Found: C, 69.93; H, 6.20; N, 3.05.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-β-oxo-3-phenoxy-(R)-Tyrosinol (141).** A solution of 1,3-bistrimethylsilyloxy-2-phenoxy-1,3-butadiene (**105**) (0.18 g, 0.56 mmol) and alkyne **120** (0.12 g, 0.42 mmol) in 3 mL of toluene was heated at reflux for 24 h. The solvent was removed in vacuo. The reaction mixture was treated with a mixture of 8 mL of THF and 2 mL of 0.5 N HCl at rt for 1 h. The aqueous phase was extracted by ethyl ether. The organic phase was washed with brine and dried over $MgSO_4$. The final phenol was obtained by flash chromatography on silica gel with 40/60 EtOAc/hexane to provide only one regioisomer **141** (90 mg, a white foam) in 48% yield: IR (film) 3500-3200, 3076, 2987, 2880, 1698, 1604, 1587, 1515, 1490, 1456, 1352, 1263, 1098, 1051, 957, 838, 753 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ

major isomer 6.98-7.60 (m, 12 H), 6.34 (s, 1 H), 5.29 (dd, $J$ = 7.5, 3.3 Hz), 4.99 (q, 2 H, $J$ = 12.3 Hz), 4.24 (t, 1 H, $J$ = 7.5 Hz), 3.93 (dt, 1 H, $J$ = 9.0, 3.3), 1.60 and 1.74 (2 s, 6 H), minor isomer 6.38 (s, 1 H), 5.39 (q, $J$ = 7.5, 3.3 Hz), 5.16 (q, 2 H, $J$ = 12.3 Hz), 1.52 and 1.67 (2 s, 6 H); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ major isomer 193.25, 155.61, 152.20, 151.76, 144.51, 136.21, 130.21, 128.57, 128.26, 128.01, 127.58, 125.35, 124.62, 118.70, 117.98, 115.92, 95.65, 66.74, 66.51, 61.90, 25.48, 24.63; minor isomer 192.65, 152.85, 144.58, 136.11, 128.69, 127.79, 128.43, 128.15, 127.86, 125.52, 124.55, 118.86, 94.97, 67.58, 66.07, 25.74, 24.46.

Anal. Calcd for $C_{26}H_{25}NO_6$: C, 69.78; H, 5.64; N, 3.13. Found: C, 69.62; H, 5.71; N, 2.89.

**N-Benzyloxycarbonyl-N,O-isopropylidenyl-β-oxo-O-methyl-3-phenoxy-(R)-tyrosinol (142).** A solution of the above aryl ether (65 mg, 0.13 mmol), $K_2CO_3$ (56 mg, 0.40 mmol), MeI (0.2 mL, excess) in DMF (2 mL) was stirred at rt overnight, then diluted with EtOAc/water (50 mL/10 mL). The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by flash chromatography on silica gel with 30/70 EtOAc/hexane to provide **142** (55 mg, a white foam) in 91% yield: $^1H$ NMR and TLC were superimposable to the above sample **140a**.

**Diels-Alder adduct 143a and 144a.** A solution of 2-methoxy-3-aryloxy-1,3-butadiene **93b** (1.9 g, 4.9 mmol) and alkyne **120** (2.0 g, 7.0 mmol) in 3 mL of toluene was heated at 120 °C (oil temperature) in a sealed glass tube for 50 h. The reaction mixture was subjected to flash chromatography on silica gel with 30% ethyl acetate in hexane to provide two regioisomers (ratio = 1:1): 1.53 g

(46% yield) of **143a** ($R_f$ 0.16, an oil) and 1.50 g (45% yield, an oil) of **144a** ($R_f$ 0.27) in 91% yield.

**Diels-Alder adduct 143b and 144b.** A solution of 2-methoxy-3-aryloxy-1,3-butadiene **93b** (0.40 g, 1.03 mmol) and alkyne **119** (0.40 g, 1.39 mmol) in 1 mL of toluene was heated at 120 °C (oil temperature) in a sealed glass tube for 36 h. The reaction mixture was subjected to flash chromatography on silica gel with 30% ethyl acetate in hexane to provide two regioisomers (ratio = 1:1): 0.26 g (37% yield) of **143b** ($R_f$ 0.16, an oil) and 0.23 g (33% yield) of **144b** ($R_f$ 0.26, an oil) in 70% overall yield.

**Oxidation of 143 and 144 by DDQ. A Typical Procedure:** The cyclohexadiene (1.53 g, 2.25 mmol, $R_f$ 0.16) was oxidized with DDQ (0.53 g, 1.05 equivs) in benzene (35 mL) at reflux for 2.5 h. The solvent was removed in vacuo, and residue was purified by flash chromatography with gradient elution (5-30% EtOAc/hexane) to provide 1.45 g of product in 95% yield.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl phenoxy]-4-methoxyphenyloxo]oxazolidine (145a).** Product obtained as a white foam: $[\alpha]_D$ +23° (c 0.98, MeOH); IR (film) 2977, 2940, 1697, 1600, 1507, 1391, 1366, 1263, 1234, 1172, 1138, 1093, 1052, 1017, 912, 836, 766, 733 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, $J$ = 8.0, 1.2 Hz, H-6 of one rotamer), 7.64 (dd, $J$ = 8.0, 2.1 Hz, H-6 of other rotamer), 7.54 (d, $J$ = 1.2 Hz, H-2 of one rotamer), 7.49 (d, $J$ = 2.1 Hz, H-2 of other rotamer), 6.86-7.27 (series of m, 10 H, Tyr aryl, H-5, Cbz aryl), 5.31 and 5.41 (two m, 1 H, oxazolidine H-4), 5.00 and 5.13 (two $A_2B_2$ q, 2 H, Cbz benzylic), 4.29 (t, 1 H, $J$ = 7.8 Hz, CH*H*O),

4.08 (m, 0.5 H, Tyr α H), 3.98 (m, 1.5 H, CH*H*O plus Tyr α H), 3.92 (s, 3 H, OMe), 3.78 (m, 2 H, $CH_2O$), 3.14 (2 due to rotamers, 1 H, $J$ = 13, 12 Hz, benzyl H), 2.66 (t, 1 H, $J$ = 12 Hz, benzyl H), 1.47-1.76 (series of 5 s due to Me groups of two rotamers, 6 H), 1.53 (s, 9 H, *t*-Bu); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ major isomer 190.20, 155.63, 155.46, 152.70, 151.65, 145.71, 136.15, 133.44, 130.77, 128.49, 128.18, 127.71, 127.50, 125.52, 118.09, 117.66, 111.77, 95.53, 94.00, 80.08, 67.74, 66.63, 65.97, 60.96, 59.24, 56.12, 38.80, 28.53, 26.81, 25.71, 24.60, 24.37; minor isomer 192.68, 155.58, 151.58, 152.10, 145.83, 136.07, 130.50, 128.07, 127.64, 125.64, 94.84, 93.50, 79.66, 66.42, 65.82, 61.84, 37.73, 28.43, 27.47, 25.47, 24.47, 23.18.

Anal. Calcd for $C_{38}H_{46}N_2O_9$: C, 67.63; H, 6.88; N, 4.15. Found: C, 67.48; H, 6.84; N, 4.01.

**(4S)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)methylphenoxy]-4-methoxyphenyloxo]oxazolidine (145b).** Product obtained as a white foam: $[\alpha]_D$= -39° (c 0.90, $CHCl_3$); $^1H$ NMR and TLC were similar to the above sample.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[4-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl) methylphenoxy]-3-methoxyphenyloxo]oxazolidine (146a).** Product obtained as a white foam: $[\alpha]_D$ +15° (c 1.02, MeOH); IR (film) 3063, 2980, 2937, 2875, 1696, 1591, 1505, 1456, 1386, 1269,1201, 1174, 1094, 1053, 947, 912, 845, 839, 756 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.68 (s, H-6 of one rotamer), 7.57 (s, H-6 of other rotamer), 6.80-7.37 (series of m, 10 H, Tyr aryl, H-5, Cbz aryl), 5.41 and 5.51 (two dd, $J$ = 7.5, 3.3 Hz, 1 H, oxazolidine H-4), 5.04 and 5.20 (two

$A_2B_2$ q, 2 H, Cbz benzylic), 4.33 (dt, $J$ = 7.5, 1.5 Hz) 4.15 (m, 0.5 H, Tyr α H), 4.02 (m, 1.5 H, CH*H*O plus Tyr α H), 3.91 and 3.93 (2 s, 3 H, OMe), 3.79 (m, 2 H, $CH_2O$), 3.14 (2 due to rotamers, 1 H, $J$ = 13, 12 Hz, benzyl H), 2.66 (t, 1 H, $J$ = 12 Hz, benzyl H), 1.47-1.81 (series of 5 s due to Me groups of two rotamers, 6 H), 1.53 (s, 9 H, *t*-Bu); $^{13}C$ NMR (69.70 MHz, $CDCl_3$) δ major isomer 193.63, 154.55, 154.26, 152.39, 151.38, 150.69, 135.95, 133.90, 130.59, 128.23, 127.88, 127.62, 127.28, 121.61, 118.70, 117.83, 111.79, 95.23, 93.73, 79.30, 66.32, 66.20, 65.71, 60.82, 58.71, 55.66, 38.61, 28.22, 27.15, 25.48, 24.36, 24.16; minor isomer 193.20, 154.35, 151.78, 151.30, 151.01, 134.08, 130.39, 127.80, 127.45, 121.84, 117.40, 111.96, 94.54, 93.24, 79.71, 67.09, 61.65, 58.46, 37.55, 28.15, 26.49, 25.22, 24.27, 22.92.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl) methylphenoxy]-4-methoxyphenylhydroxymethyl] oxazolidine (147a).** To the above ketone **145a** (0.35 g, 0.52 mmol) in 12 mL of MeOH cooled to 0 °C was added sodium borohydride (40 mg, 1.0 mmol), and the mixture was stirred at the same temperature for 2 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel using 30% ethyl acetate in hexane as eluent to give the alcohol (0.32 g, a white foam) in 91% yield: $[\alpha]_D$ +5° (c 0.40, $CHCl_3$); IR (film) 3450 (br), 2980, 2937, 1698 (br), 1610, 1507, 1456, 1391, 1366, 1352, 1259, 1225, 1170, 1126, 1093, 1051, 1029, 947, 853 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.74-7.40 (m, 12 H), 5.12 (s, 2 H, $PhCH_2$), 4.68 (m, 1 H), 4.20 (m, 1 H), 3.82 (s, 3 H, Me), 3.64-4.10 (m, 5 H), 3.15 (2 d due to

rotamers, 1 H, benzyl H), 2.62 (dt, 1 H, benzyl H), 1.42-1.60 (series of s due to Me groups of two rotamers, 6 H), 1.45 (s, 9 H, *t*-Bu).

**(4S)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl phenoxy]-4-methoxyphenylhydroxymethyl]oxazolidine (147b).** To the above ketone **145b** (0.21 g, 0.31 mmol) in 6 mL of MeOH cooled to 0 °C was added sodium borohydride (20 mg, 0.5 mmol), after which the mixture was stirred at the same temperature for 2 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel using 30% ethyl acetate in hexane as eluent to give the alcohol (0.17 g, a white foam) in 81% yield: $[\alpha]_D$ -15° (c 0.40, $CHCl_3$); $^1H$ NMR and TLC were similar to the above sample **147a**.

**(4S)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl phenoxy]-4-methoxyphenylmethyl]oxazolidine (149a).** A solution of benzyl alcohol **147a** (0.31 g, 0.46 mmol), thiocarbonyl diimidazole (0.14 g, 0.69 mmol) and DMAP (50 mg) in 12 mL of 1,2-dichloroethane was heated at reflux under nitrogen for 15 h. Flash chromatography on silica gel with elution by 40% ethyl acetate in hexane followed by 60% ethyl acetate in hexane furnished 0.27 g (78% yield, a yellow foam) of the corresponding imidazole thiocarbonyl ester **148a**: IR (film) 2981, 2938, 2883, 1765, 1698, 1609, 1585, 1506, 1470, 1392, 1366, 1351, 1272, 1224, 1170, 1095, 1074, 1052, 962, 884, 850, 808, 700 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.98-8.16 (3 s, 1 H), 6.82-7.45 (m, 14 H), 5.10-5.35 (m, 3 H), 4.40 (2 br m, 1 H), 3.78 (br s, 3 H, Me), 3.75-4.15 (m, 5 H), 3.15 (2 d due to

rotamers, 1 H, Tyr-CH*H*), 2.62 (dt, 1 H, Tyr-CH*H*), 1.42-1.60 (series of s due to Me groups of two rotamers, 6 H), 1.50 (s, 9 H, *t*-Bu).

A solution of the above ester **148a** (0.27 g, 0.36 mmol), AIBN (8 mg) and tributyltin hydride (0.80 mL) in 5 mL of toluene was degassed with nitrogen for 10 min, after which the mixture was heated at reflux for 2.5 h. Flash chromatography on silica gel with elution by 5-30% ethyl acetate in hexane furnished **149a** (0.21 g) as a white foam (87% yield): $[\alpha]_D$ -28° (c 0.87, EtOAc); IR (film) 2935, 1696 (br), 1609, 1506, 1455, 1386, 1258, 1171, 1129, 1094, 1029, 968, 857, 762 $cm^{-1}$; $^1H$ NMR 6.75-7.36 (m, 11 H, aromatic Hs), 5.15 (2 s, 2 H, due to two rotamers), 3.95-4.15 (br m, 2 H, two α H), 3.80 (s, 3 H, Me), 3.77 (br s, 4 H, 2 x $CH_2O$), 2.90-3.30 (m, 2 H, Tyr benzylic), 2.60 (br q, 2 H, Tyr benzylic), 1.52 (br s, 9 H, Boc), 1.43-1.62 (series of s, 6 H, 2 x Me).

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-(4S)-(3-*t*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl) methylphenoxy]-4-methoxyphenylmethyl]oxazolidine (149b).** The benzyl alcohol **147b** (0.16 g, 0.24 mmol), thiocarbonyl diimidazole (64 mg, 0.36 mol, 1.5 equiv) and DMAP (15 mg, 0.12 mmol, 0.5 equiv) in 6 mL of 1,2-dichloroethane were heated at reflux under nitrogen for 10 h. Flash chromatography on silica gel with elution by 40% ethyl acetate in hexane, followed by 60% ethyl acetate in hexane, furnished 0.12 g (66% yield, a yellow foam) of the corresponding imidazole thiocarbonyl ester **148b**. $^1H$ NMR and TLC were similar to the above sample **149a**.

A solution of the above ester **147b** (0.12 g), AIBN (6 mg) and tributyltin hydride (0.40 mL) in 2 mL of toluene was degassed with

nitrogen for 10 min, after which the mixture was heated at reflux for 2 h. Flash chromatography on silica gel with elution by 5-30% ethyl acetate in hexane furnished 80 mg of **149b** as a white foam (88% yield): $[\alpha]_D$ 6.6° (c 1.40, $CHCl_3$); $^1H$ NMR and TLC were similar to the above sample **149a**.

**Mosher's amides 150a and 150b. A Typical procedure:** A solution of **149b** (**149a**, **169**) (24 mg, 0.036 mmol) and PhSMe (15 mg, ~3 equiv) in 1 mL of $CH_2Cl_2$ was cooled to 0 °C and added 0.5 mL of $CF_3CO_2H$. The reaction mixture was warmed up to rt for 1 h, and the solvent was removed in vacuo. The residue was dried in vacuo for 1-2 h.

To the above residue in 1 mL of $CH_2Cl_2$ at rt was added DMAP (27 mg, ~6 equiv) and $Ac_2O$ (19 μL, 5 equiv). The reaction mixture was stirred overnight, and the solvent was removed in vacuo. The residue was taken up in EtOAc/1 N HCl (15 mL/3 mL). The organic layer was washed with brine, $NaHCO_3$ (saturated) and brine and dried over $MgSO_4$. The ester was purified on MPLC (silica gel) using 40% ethyl acetate in hexane to provide 11 mg (50% yield). The $^1H$ NMR spectrum of the ester was consistent with the assigned structure.

To the above 11 mg (0.018 mmol) of the ester was added 0.5 mL of HBr in HOAc at rt for 1 h. The acetic acid was removed in vacuo. The residue was coevaporated with heptane and dried in high vacuo for 1-2 h, then dissolved in 1 mL of $CH_2Cl_2$. The solution was cooled to 0 °C, followed by addition of Mosher's acid (0.018 mmol, 1.0 equiv), HOBt (0.018 mmol, 1.0 equiv), $Et_3N$ (0.036 mmol, 1.0 equiv) and EDCI (0.027 mmol, 1.5 equiv). The reaction mixture was stirred

in 0 °C for 2-3 h and rt overnight. The solvent was removed in vacuo. The residue was dissolved in EtOAc/$H_2O$. The organic phase was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine and dried over $MgSO_4$.

$^1H$ NMR spectra of the crude products showed that chemical shift of methoxy group of Mosher's amide for (S,S)-tyrosinol **149a** or **169** was 3.28 ppm, while that for (R,S)-tyrosinol **149b** was 3.32 ppm. $^1H$ NMR analysis of an admixture of Mosher's amides **150a** and **150b** established the clean resolution of the diastereotopic O-methyl peaks of the Mosher's amides.

**Mosher's amide 151.** A solution of diol **155a** and $Pd(OH)_2$ in 0.5 mL of THF and 0.5 mL of MeOH was stirred under $H_2$ gas at rt for 4 h. The solution was subjected to a short Celite pad. The solvent was removed in vacuo, and the residue was dried in vacuo for 1-2 h.

To the above free amino alcohol (~8 mg) in $CH_2Cl_2$ (1 mL) at 0 °C was added Mosher's acid (4 mg, ~1 equiv), TEA (2 μL, ~0.5 equiv), HOBt (3 mg, ~1 equiv) and EDCI (4 mg, ~1 equiv). The reaction mixture was stirred in 0 °C for 2-3 h and rt overnight. The solvent was removed in vacuo. The residue was dissolved in EtOAc/$H_2O$. The organic phase was washed with 1 N HCl, $NaHCO_3$ (saturated) and brine, then dried over $MgSO_4$. The residue was purified on MPLC on silica gel using 50% ethyl acetate in hexane to provide ~5 mg of amide **151**: $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.75-7.50 (12 H, aromatic Hs), 4.75 (br s, 1 H, NH), 4.15 (br m, 1 H, α H), 3.84 (s, 3 H, OMe), 3.82 (br m, 1 H, α H), 3.50-3.70 (m, 4 H, 2 x $OCH_2$), 3.27 (s, 3 H, OMe), 2.80 (br, m, 4 H, Tyr benzylic), 1.42 (s, 9 H, Boc).

**Mosher's amide 152.** To a solution of amide **151** and DMAP (5 mg) in 0.5 mL of $CH_2Cl_2$ at 0 °C was added by 10 μL of $Ac_2O$. The reaction mixture was warmed up to rt and stirred overnight. The solvent was removed in vacuo and the residue was purified on a short silica gel pad to provide enough sample for NMR: $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.80-7.50 (12 H, aromatic Hs), 4.85 (br s, 1 H, NH), 4.42 (br s, 1 H, α H), 4.00-4.15 (m, 5 H), 3.82 (s, 3 H, OMe), 3.50-3.29 (s, 3 H, OMe), 2.80 (br q, 4 H, Tyr benzylic), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.45 (s, 9 H, Boc).

**N-Benzyloxycarbonyl-O-methyl-3-[4-[(2S)-2-(*t*-butyloxycarbonylamino)-3-hydroxypropyl]phenoxy]-(S)-tyrosinol (155a).** Diaryl ether **149a** (69 mg) in 1 mL of MeOH containing 5 mg of p-toluenesulfonic acid monohydrate was stirred at rt for 4 h. TLC analysis (EtOAc/hexane = 4:1) showed small amounts of monoalcohol and diol present. Work-up in standard fashion, followed by MPLC on silica gel by elution with 30% and 60% ethyl acetate in hexane, gave a mixture of monoalcohol **153** and **154** (23 mg, a white foam) and diol **155a** (35 mg, a white foam) in 57% overall yield: $[\alpha]_D$ -26° (c 0.95, $CHCl_3$); IR (film) 3200-3450, 2933, 1694, 1609, 1586, 1505, 1444, 1368, 1270, 1169, 1129, 1052, 969, 820, 752 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.70-7.33 (m, 12 H, aromatic Hs), 5.06 (s, 2 H, $PhCH_2$), 5.05 (br s, 1 H, NH), 4.80 (br d, 1 H, NH), 3.82 (s, 3 H, OMe), 3.50-3.70 (m, 4 H, $OCH_2$), 2.75 (m, 4 H, $CH_2$), 1.41 (s, 9 H, Boc).

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[[4-(2S)-2-*t*-butyloxycarbonyl)amino-3-hydroxypropyl]phenoxy]-4-**

**methoxyphenyloxo]oxazolidine (158a).** Diaryl ether **145a** (1.40 g, 2.07 mmol) in 40 mL of MeOH containing 180 mg of p-toluenesulfonic acid monohydrate was stirred at rt for 2.5 h. TLC analysis (EtOAc/Hexane = 3:2) showed small amounts of **145a** and diol present. Work-up in standard fashion, followed by MPLC on silica gel by elution with 30% and 60% ethyl acetate in hexane, gave 0.91 g of **158a** as a white foam in 69% yield; reactant (0.15 g) and corresponding diol (0.06 g, a white foam) were also isolated: $[\alpha]_D$ +18° (c 1.00, $CHCl_3$); IR (film) 3390, 2978, 2938, 1703, 1600, 1506, 1457, 1421, 1360, 1345, 1266, 1170, 1138, 1123, 1096, 1050, 911, 837, 788, 760 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.84-7.74 (series of m, 12 H, aromatic Hs), 5.32 and 5.40 (two m, 1 H, oxazolidine H-4), 5.03 and 5.16 (two $A_2B_2$ q, 2 H, Cbz benzylic), 4.78 (br m, 1 H, NH), 4.29 (m, 1 H, $CH_2OH$), 3.97 (m, 1 H, $CH_2OH$), 3.92 (s, 3 H, OMe), 3.85 (br m, 1 H, α H), 3.65 and 3.68 (dd, 1 H, $J$ = 11.1, 3.6 Hz, oxazolidine H-5), 3.53 and 3.57 (dd, 1 H, $J$ = 11.1, 5.3 Hz, oxazolidine H-5), 2.81 (d, 2 H, $J$ = 7.2 Hz, benzyl Hs), 2.14 (br s, 1 H, OH), 1.61 and 1.76 (2 s, Me, major rotamer), 1.54 and 1.68 (2 s, Me, minor rotamer, 6 H for both rotamers), 1.42 (s, 9 H, *t*-Bu); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ major isomer 193.20, 156.07, 155.49, 152.73, 151.68, 145.56, 136.10, 132.79, 130.54, 128.50, 128.19, 127.91, 127.49, 125.67, 119.94, 117.59, 111.80, 95.53, 79.63, 66.65, 66.41, 63.99, 60.96, 56.13, 53.62, 36.52, 28.30, 24.61, 24.36; minor isomer 192.68, 155.67, 145.68, 136.27, 128.08, 127.83, 127.72, 125.94, 117.82, 94.86, 67.47, 65.96, 61.84, 25.71, 25.39.

Anal. Calcd for $C_{35}H_{42}N_2O_9 \cdot H_2O$: C, 64.39; H, 6.80; N, 4.29. Found: C, 64.38; H, 7.00; N, 3.99.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[4-[[4-(2S)-2-(*t*-butyloxycarbonyl)amino-3-hydroxypropyl]phenoxy]-3-methoxyphenyloxo]oxazolidine (159a).** Diaryl ether **146a** (1.47 g, 2.17 mmol) in 40 mL of MeOH containing 190 mg of p-toluenesulfonic acid monohydrate was stirred at rt for 3 h. TLC analysis (EtOAc/hexane = 3 : 2) showed small amounts of **146a** and diol present. Work-up in standard fashion, followed by MPLC on silica gel by elution with 30% and 60% ethyl acetate in hexane, gave 1.00 g of monoalcohol **159a** as a white foam in 73% yield: $[\alpha]_D$ +5.8° (c 0.97, MeOH); IR (film) 3350-3500, 3035, 2981, 2937, 1707, 1591, 1505, 1456, 1416, 1367, 1268, 1169, 1099, 1099, 1053, 912, 885, 838, 764 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.85-7.68 (series of m, 12 H, aromatic Hs), 5.48 and 5.40 (two dd, 1 H, *J* = 7.5, 3.3 Hz, oxazolidine H-4), 5.14 and 5.04 (two $A_2B_2$, 2 H, Cbz benzylic), 4.75 (br d, 1 H, NH), 4.32 (dt, *J* = 7.5, 1.8 Hz, 1 H, $CH_2OH$), 4.01 (dt, *J* = 9.0, 3.3 Hz, 1 H, $CH_2OH$), 3.93 and 3.91 (2 s, 3 H, OMe), 3.85 (br m, 1 H, α H), 3.67 (dd, *J* = 10.5, 2.7 Hz, oxazolidine H-5), 3.55 (dd, 1 H, *J* = 11.1, 5.1 Hz, oxazolidine H-5), 2.83 (d, 2 H, *J* = 6.6 Hz, benzyl Hs), 2.24 (br s, 1 H, OH), 1.63 and 1.80 (2 s, Me, major rotamer), 1.56 and 1.74 (2 s, Me, minor rotamer, 6 H for both rotamers), 1.42 (s, 9 H, *t*-Bu); $^{13}C$ NMR (75.44 MHz, $CDCl_3$) δ major isomer 193.80, 155.83, 154.13, 152.66, 151.62, 150.51, 135.89, 134.02, 130.55, 128.34, 128.02, 127.94, 127.73, 127.36, 121.73, 118.97, 111.75, 95.39, 79.29, 66.56, 66.28, 63.44, 60.91, 55.82, 53.50, 36.55, 28.00, 25.57, 24.49; minor isomer 193.34, 154.21, 151.24, 135.82, 133.89, 129.89, 128.21, 127.89, 127.84, 127.60, 121.97, 117.22, 111.97, 94.76, 67.35, 65.83, 61.77, 25.23, 24.23.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-[(2S)-2-*t*-butyloxycarbonyl)amino-3-(*t*-butyldimethylsilyloxy)-propyl]phenoxy]-4-methoxyphenylhydroxymethyl] oxazolidine (166).** Alcohol **158a** (0.60 g, 0.94 mmol) in 8 mL of $CH_2Cl_2$ at 0 °C was treated with TBDMSiCl (150 mg, 1.0 mmol), DMAP (12 mg, 0.1 mmol) and triethylamine (278 μL, 2.0 mmol). The mixture was stirred at 0 °C for 2 h and at rt for 1 h. TLC analysis indicated the reaction was not complete, and an additional 45 mg of TBDMSiCl and 85 μL of triethylamine were added. After stirring overnight, the solvent was removed in vacuo and the residue purified by flash chromatography on silica gel using 40% ethyl acetate in hexane as eluent to give the silyl ether **165** as a white foam in quantitative yield (0.70 g): IR (film) 2934, 2857, 1714, 1600, 1506, 1410, 1365, 1264, 1172, 1098, 1066, 837, 779, 734 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.83-7.73 (series of m, 12 H, aromatic Hs), 5.40 (dd, $J$ = 7.2, 3.0 Hz, 0.4 H, oxazolidine H-4), 5.31 (dd, $J$ = 7.5, 3.3 Hz, 0.6 H, oxazolidine H-4), 5.01 and 5.17 (two $A_2B_2$ q, 2 H, Cbz benzylic), 4.75 (br d, 1 H, NH), 4.28 (t, $J$ = 8.1 Hz) 3.95 (dt, $J$ = 3.0, 9.0 Hz, CH*H*O), 3.83 (br m, 1 H, CH*H*O), 3.52 (m, 2 H, $CH_2O$), 2.81 (d, $J$ = 6.9 Hz, 2 H, Tyr benzylic), 1.60 and 1.76 (2 s, Me, major rotamer), 1.52 and 1.69 (2 s, Me, minor rotamer, 6 H for both rotamers), 1.42 (s, 9 H, *t*-Bu), 0.88 (s, 9 H, Si*t*-Bu), 0.05 (s, 6 H, $SiMe_2$); $^{13}C$ NMR (67.90 MHz, $CDCl_3$) δ major isomer 193.38, 155.87, 155.57, 155.52, 151.89, 145.97, 136.39, 133.58, 130.86, 128.41, 128.15, 127.74, 127.92, 125.68, 120.09, 117.76, 112.05, 95.76, 79.35, 67.64, 66.85, 63.08, 61.12, 56.24, 53.18, 36.70, 28.56, 26.07, 25.67, 24.63, 18.42, -5.25; minor isomer 192.88, 152.91, 136.34, 133.53,

128.70, 128.28, 125.83, 117.95, 95.07, 67.48, 66.65, 62.08, 61.27, 56.40, 25.93, 24.81.

To the above silyl ether (0.60 g, 0.80 mmol) in 12 mL of MeOH cooled to 0 °C was added sodium borohydride (50 mg, 1.2 mmol), and the mixture was stirred at the same temperature for 2 h. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel using 30% ethyl acetate in hexane as eluent to give the alcohol (0.56 g) as a white foam in 93% yield: IR (film) 2933, 2860, 1703, 1610, 1507, 1459, 1409, 1352, 1259, 1226, 1170, 1126, 1096, 1070, 1030, 912, 838, 778, 735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5 H), 7.15 (d, 2 H), 7.01 (m, 3 H), 6.88 (d, 2 H), 4.72 and 4.79 (two m, 1 H each, NH or oxazolidine H-4), 4.21 (m, 1 H), 3.84 (s, 3 H, OMe), 3.66-3.78 (m, 3 H, $CH_2O$, Tyr α H), 3.52 (m, 2 H, $CH_2O$), 2.81 (d, $J$ = 7.2 Hz, 2 H, Tyr benzylic), 1.48 and 1.51 (2 s, Me, 6 H, oxazolidine Me), 1.45 (s, 9 H, Boc), 0.94 (s, 9 H, Si*t*-Bu), 0.062 (s, 6 H, $SiMe_2$).

Anal. Calcd for $C_{41}H_{58}NO_9Si$: C, 65.56; H, 7.80; N, 3.73. Found: C, 65.52; H, 7.68; N, 3.64.

**(4R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-[3-[4-[(2S)-2-(*t*-butyloxycarbonyl)amino-3-hydroxypropyl]phenoxy]-4-methoxyphenylmethyl]oxazolidine (169).** Benzyl alcohol (90 mg, 0.12 mmol), thiocarbonyl diimidazole (50 mg) and DMAP (8 mg) in 2 mL of 1,2-dichloroethane were heated at reflux under nitrogen for 10-11 h. Flash chromatography on silica gel with elution by 40% ethyl acetate in hexane, followed by 60% ethyl acetate in hexane, furnished 65 mg as a yellow foam (63% yield) of the imidazole thiocarbonyl ester **167**: IR (film) 3536-3437, 3033, 2933,

1707, 1609, 1586, 1506, 1471, 1403, 1366, 1350, 1272, 1222, 1170, 1129, 1098, 1072, 1028, 967, 885, 838, 735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.95, 8.10 and 8.15 (three br s, 1 H, imidazole H-2, due to different isomers or rotamers), 6.87-7.40 (series of m, 14 H, aryl + 2 imidazole Hs), 5.02-5.36 (series of m, 3 H, Cbz benzylic + 1 H) 4.75 (m, 1 H, NH), 4.37 and 4.47 (two m, 1 H, α H), 3.95 (m, 3 H, $CH_2O$, α H), 3.80 and 3.81 (two s, 3 H, OMe), 3.51 (m, 2 H, $CH_2O$), 2.79 (d, 2 H, Tyr benzylic), 1.30, 1.36, 1.49 (series of s, oxazolidine Me),1.47 (s, 9 H, Boc), 0.92 (s, 9 H, Si*t*-Bu), 0.046 (s, 6 H, $SiMe_2$).

The above ester (65 mg, 0.075 mmol), AIBN (7 mg) and tributyltin hydride (0.45 mL) in 1.5 mL of toluene were degassed with nitrogen for 10 min, after which the mixture was heated at reflux for 2 h. Flash chromatography on silica gel with elution by 20% ethyl acetate in hexane furnished 54 mg as a white foam (96% yield) of the silyl ether of isodityrosinol **168**: IR(film) 3385 (br), 2953, 2930, 1708 (br) 1609, 1586, 1507, 1471, 1407, 1365, 1354, 1257, 1169, 1129, 1072, 1057, 968, 838 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.75-7.37 (12 H, aromatic Hs), 5.13 and 5.20 (2 s, 2 H, Cbz benzylic), 4.85 (br d, 1 H, NH), 3.95-4.15 (two br m, 1 H, α H), 3.81 (s, 3 H, OMe), 3.79 (br m, 3 H, $OCH_2$ + α H), 3.53 (br s, $OCH_2$), 2.95 and 3.15 (four br s, 1 H, Tyr benzylic), 2.80 (br d, 2 H, $J$ = 7.2 Hz), 2.55-2.62 (dd, $J$ = 10.5, 12.6 Hz) 1.54 and 1.63 (2 s, 6 H, 2 x Me), 1.44 (s, 9 H, Boc), 0.94 (s, 9 H, $SiCMe_3$), 0.06(s, 6 H, $SiMe_2$).

The above silyl ether (54 mg, 0.074 mmol) and tributylammonium fluoride (50 mg, 0.15 mmol) were stirred at rt in 1.5 mL of THF for 1 h. The mixture was subjected to flash chromatography on silica gel, eluting by 20% ethyl acetate in hexane

and then 60% ethyl acetate in hexane, to furnish a quantitative yield (45 mg) of isodityrosinol **169** as a white foam: $[\alpha]_D$ -29° (c 1.67, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5 H), 7.13 (d, 2 H, *J* = 8.7 Hz), 6.74-6.98 (m, 5 H), 5.11 and 5.16 (two nearly superimposed $A_2B_2$ q, 2 H, Cbz benzylic), 4.77 (d, 1 H, NH), 4.03 (m, 1 H, α H), 3.73-3.84 (m, 3 H, $CH_2O$, α H), 3.79 (s, 3 H, OMe), 3.63 and 3.67 (dd, *J* = 10.8, 3.0 Hz, 1 H, CH*H*O, Tyr α H), 3.52 and 3.55 (dd, *J* = 10.8, 5.1 Hz 1 H, CH*H*O), 2.95 and 3.11 (two set of d due to two rotamers, *J* ax = 13.2 and 12.8 Hz, respectively, *J* bx = 0 Hz, 1 H, benzylic Hα), 1.50, 1.52 and 1.61 (three s, 6 H, 2 x Me), 1.45 (s, 9 H, Boc); $^{13}C$ NMR (69.70 MHz, $CDCl_3$) δ major isomer 156.58, 156.11, 152.07, 150.17, 144.79, 136.37, 131.13, 130.31, 128.51, 128.09, 127.91, 125.43, 122.04, 117.22, 116.94, 112.92, 94.35, 79.63, 66.71, 66.25, 64.06, 58.88, 56.01, 53.74, 38.69, 36.55, 28.31, 26.59, 23.14; minor isomer 156.64, 150.04, 145.10, 131.78, 121.94, 93.88, 67.08, 65.83, 59.55, 37.46, 27.49, 24.55.

Anal. Calcd for $C_{35}H_{40}N_2O_8 \cdot 0.5H_2O$: C, 67.17; H, 6.62; N, 4.48. Found: C, 66.95; H, 7.11; N, 4.21.

**N-[N-(1,1-Dimethylethyloxy)carbonyl]-O-[(R)-4-(3-benzyloxycarbonyl-2,2-dimethyloxazolidin-4-yl-oxo)-2-methoxyphenyl]-L-tyrosyl]-O-methyl-L-tyrosine α-Methyl Ester (171).** A solution of the alcohol **159a** (0.58 g, 0.91 mmol) in MeCN (10 mL), $CCl_4$ (6 mL) and $H_2O$ (6 mL) was cooled to 0 °C. $NaIO_4$ (1.58 g, 7.28 mmol, 8.0 equiv) was added, followed by $RuCl_3$ (19 mg, 0.073 mmol, 0.08 equiv). The reaction mixture was kept at 0 °C for 2 h, and TLC indicated that no alcohol remained. The mixture was diluted with 20 mL of methylene chloride. The solution was

subjected to a short Celite pad. The aqueous phase was extracted with ethyl acetate and methylene chloride. The residue was subjected to flash chromatography on silica gel as well as eluting by $CHCl_3$ and 15% acetone in $CHCl_3$, to furnish a 78% yield (0.46 g) of acid **170** (a white foam): IR (film) 3380-3560, 3079, 2983, 2933, 1711, 1591, 1504, 1465, 1413, 1384, 1368, 1267, 1202, 1170, 1098, 1052, 911, 839, 734 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.90-7.67 (series of m, 12 H, aromatic Hs), 5.48 and 5.40 (two sets of dd, 1 H, *J* = 7.8, 3.3 Hz, oxazolidine H-4), 5.19 and 5.04 (two $A_2B_2$, 2 H, Cbz benzylic), 5.00 (br d, 1 H, NH), 4.60 (m, 1 H, α H); 4.35 (dt, *J* = 7.5, 1.5 Hz, 1 H), 3.85-4.08 (m, 2 H), 3.91 and 3.90 (2 s, 3 H, OMe), 3.00-3.15 (br m, 2 H, tyrosine benzylic) 1.63 and 1.80 (2 s, Me, major rotamer), 1.56 and 1.73 (2 s, Me, minor rotamer, 6 H for both rotamers), 1.42 (s, 9 H, *t*-Bu). The acid was used directly in the next coupling reaction.

A solution of N-Boc-O-methyl-tyrosine methyl ester (0.29 g, 0.92 mmol, 1.3 equiv) in 5 mL of $CH_2Cl_2$ and 2 mL of $CF_3CO_2H$ was stirred for 1 h. The solvent was removed in vacuo, after which the residue was coevaporated with toluene twice and dried in vacuo for 1 h. To a solution of the above amino salt in 12 mL of dichloromethane was added acid **170** (0.46 g, 0.71 mmol), triethylamine (130 μL, 0.93 mmol) and HOBt (130 mg, 0.93 mmol). The solution was cooled to 0 °C before EDCI (180 mg, 0.93 mmol) was added. The reaction mixture was kept at 0 °C for 2 h and rt overnight. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate and water. The organic phase was washed with 1 N HCl, brine, $NaHCO_3$ (saturated) and brine. The tripeptide

**171** was obtained by flash chromatography on silica gel, eluting by 50% ethyl acetate/hexane, in a 51% yield (0.32 g) as a white foam: IR (film) 3300-3500, 3067, 3034, 2983, 2948, 1744, 1713, 1613, 1590, 1505, 1456, 1413, 1366, 1348, 1269, 1202, 1170, 1140, 1097, 1052, 1018, 913, 885, 839, 785 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.77-7.67 (m, 16 H, aromatic), 6.33 (br s, 1 H, NH), 5.37 and 5.50 (two sets of dd, 1 H, $J$ = 7.5, 3.3 Hz, α H), 4.98 and 5.23 (two sets of $A_2B_2$, 2 H, Cbz, $J$ = 12.5), 4.97 (br s, 1 H, NH), 4.76 (dd, 1 H, $J$ = 6.0, 12.6 Hz), 4.32 (dt, 1 H, $J$ = 9.0, 1.5 Hz), 3.99-4.02 (dt, 1 H, $J$ = 9.0, 7.5 Hz), 3.91 and 3.89 (2 s, 2 H), 3.77 (s, 3 H, Me), 3.68 (s, 3 H, Me), 3.02 (m, 4 H) 1.81, 1.74, 1.63, 1.54 (4 s, 6 H, 2 x Me), 1.42 (s, 9 H, Boc); $^{13}C$ NMR (69.70 MHz, $CDCl_3$) δ major isomer 193.91, 171.44, 170.56, 158.67, 155.17, 154.89, 152.75, 151.13, 150.81, 136.18, 132.43, 130.78, 130.18, 128.98, 128.52, 128.21, 127.78, 28.44, 121.81, 119.18, 117.67, 113.96, 111.95, 95.62, 80.21, 66.69, 66.48, 66.02, 61.09, 56.0, 55.11, 53.32, 52.24, 37.61, 37.04, 28.20, 24.65, 24.41; minor isomer 193.51, 155.14, 154.99, 151.72, 136.11, 132.30, 130.26, 128.10, 127.94, 127.44, 122.07, 117.79, 114.01, 112.16, 94.92, 80.18, 67.48, 61.89, 55.67, 53.60, 53.19, 25.73, 25.48.

Anal. Calcd for $C_{46}H_{53}N_3O_{12}$: C, 65.77; H, 6.37; N, 5.00. Found: C, 65.79; H, 6.43; N, 4.86.

**N-[N-(1,1-Dimethylethyloxy)carbonyl]-O-[(R)-5-(3-benzyloxycarbonyl-2,2-dimethyloxazolidin-4-yl-methyl)-2-methoxyphenyl]-L-tyrosyl]-O-methyl-L-tyrosine α-Methyl Ester (174).** A solution of alcohol **169** (107 mg, 0.17 mmol) in MeCN (1 mL), $CCl_4$ (0.6 mL) and $H_2O$ (0.6 mL) was cooled to 0 °C. $NaIO_4$ (300 mg, 1.40 mmol) was added, followed by $RuCl_3$ (4 mg,

0.019 mmol). The reaction mixture was kept at 0 °C for 2 h, then diluted with 15 mL of dichloromethane. The aqueous phase was extracted with 3 x 10 mL of $CH_2Cl_2$. The organic phase was passed through a short Celite pad. The solvent was removed in vacuo. The residue was subjected to flash chromatography on silica gel, eluting by chloroform, and then 15% acetone in chloroform to furnish a 81% yield (91 mg) of acid **173** (a white foam): $^1$H NMR (300 MHz, $CDCl_3$) δ 6.80-7.40 (series of m, 12 H, aromatic Hs), 5.15 (d, 2 H, Cbz benzylic), 5.05 (br d, 1 H, NH), 4.60 (m, 1 H, α H); 4.35 (m, 1 H), 3.85-4.10 (m, 2 H), 3.80(s, 3 H, OMe), 3.00-3.20 (br m, 3 H,) 2.80 (m, 1 H), 1.40-1.65 (set of s, 15 H, *t*-Bu + 2 x Me). The acid was used directly in the next coupling reaction.

A solution of N-Cbz-O-methyltyrosine methyl ester (70 mg, 0.20 mmol) in 0.8 mL of HBr/HOAc was stirred at rt for 1 h. The acid was removed in vacuo. The residue was coevaporated with toluene twice and dried in vacuo for 1 h. To a solution of the above amino salt in 2 mL of dichloromethane was added acid 173 (91 mg, 0.14 mmol), triethylamine (28 μL, 0.20 mmol) and HOBt (27 mg, 0.20 mmol). The solution was cooled to 0 °C before EDCI (39 mg, 0.20 mmol) was added. The reaction mixture was kept at 0 °C for 2 h and rt overnight. The solution was removed in vacuo, and the residue was dissolved in ethyl acetate and water. The organic phase was washed with 1 N HCl, brine, $NaHCO_3$ (saturated) and brine. The tripeptide was obtained by flash chromatography on silica gel, eluting by 40% ethyl acetate in hexane, in a 72% yield (90 mg) of the peptide **174** as a white foam: IR (film) 3300-3500, 3033, 2979, 2954, 2837, 1744, 1705, 1613, 1585, 1514, 1443, 1408, 1354, 1251,

1175, 1129, 1096, 1057, 1030, 968, 911, 841, 766, 734 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.79-7.36 (m, 16 H), 6.30 (br s, 1 H, NH) 5.11 and 5.16 (2 s, 2 H), 4.95 (br s 1 H, NH) 4.75 (m, 1 H, α H), 4.30 (m, 1 H), 4.00 (m, 1 H), 3.68-3.77 (sets of s, 11 H, 3 x Me, $CH_2$), 2.99 (m, 5 H), 2.54-2.62 (dd, $J$ = 12.5, 10.5 Hz), 1.61 and 1.50 (2 s, 6 H, 2 x Me), 1.40 (s, 9 H, Boc); $^{13}C$ NMR (69.70 MHz, $CDCl_3$) δ major isomer 171.44, 170.72, 158.69, 157.13, 155.25, 152.10, 150.30, 144.48, 136.40, 131.25, 130.44, 130.21, 128.60, 128.54, 128.12, 127.96, 125.67, 122.39, 116.81, 114.03, 113.96, 112.97, 94.37, 80.19, 66.73, 66.28, 58.88, 55.98, 55.71, 55.14, 53.40, 52.24, 38.71, 37.36, 37.09, 28.22, 26.63, 23.16; minor isomer 158.72, 136.36, 130.31, 128.78, 127.53, 125.77, 117.01, 113.05, 93.88, 67.06, 65.89, 59.55, 55.74, 55.19, 36.98, 27.49, 24.58.

Anal. Calcd for $C_{46}H_{55}N_3O_{11}$: C, 66.88; H, 6.72; N, 5.09. Found: C, 66.59; H, 6.65; N, 4.91.

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# CURRICULUM VITAE

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